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CHAPTER 33

Systemic Autoimmunity

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The study of systemic autoimmune disease has held the interest of many immunologists for two important reasons. First, human systemic autoimmune diseases are an important cause of suffering and shortening of life. Second, the aberrations that lead to autoreactivity against multiple self antigens must hold the keys to understanding important aspects of the fundamental basis of self–nonself discrimination.

Systemic autoimmunity is mediated both by autoantibodies and by self-reactive T cells. The availability of human autoimmune sera and autoantigen-binding monoclonal antibodies has yielded considerable insight into the nature of autoantibodies and their binding to antigen. More recently, hybridoma technology has extended this knowledge to immunoglobulin genetics, mostly using autoantibodies derived from mice. The cellular basis for autoantibody formation, especially the participation of helper T-lymphocytes in these responses, has been much harder to study. In part, this reflects the difficulties of investigation in humans, the practical difficulties of studying cells versus serum, and the inadequacy of animal models. It seems likely that direct autoreactive T-cell injury is an important

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part of many of the autoimmune diseases discussed below, but currently there is a poor understanding of the specificity and the regulation of T cells mediating systemic autoimmune disease.

A large number of potential etiologies have been put forth to explain systemic autoimmune disease. It seems unlikely that a single explanation is adequate to account for the diverse phenomena described in this chapter, yet there are common issues regarding self-reactive immune responses, regardless of the inciting causes. The comments regarding overall mechanisms of autoimmune disease may not apply to all diseases or models, but are intended to place systemic autoreactivity into the context of basic immunology and to focus future thought about mechanisms.

GENERAL CONSIDERATIONS

Systemic autoimmunity encompasses autoimmune conditions in which autoreactivity is not limited to a single organ or organ system. This definition would include systemic lupus erythematosus (SLE), systemic sclerosis (scleroderma), rheumatoid arthritis (RA), chronic graft-versus-host disease (GVHD), and the various forms of vasculitis. A truly satisfactory definition is elusive; the demonstration of autoimmunity as a cause of disease is difficult

and requires the replication of disease manifestation by transfer of antibody or T-lymphocytes. As these kinds of data are difficult to generate, the inference that a disease is autoimmune is made based on the presence of autoantibodies and the localization in diseased tissue of antibody, complement, and T-lymphocytes.

In addition to the human diseases, there are many animal models that are helpful in testing hypotheses about human illness and in gaining insights into fundamental mechanisms; however, some models may not be not representative of human diseases.

Certain features of systemic autoimmune disease stand out as clues to the possible etiology. The first is their variable course from person to person (or even from inbred mouse to inbred mouse) and their tendency to wax and wane in severity over time. In a single individual, disease activity can vary from life-threatening to asymptomatic, even without medical intervention. This suggests the operation of potent forces that can downregulate the autoimmune process.

A second characteristic of most systemic autoimmune conditions is the increased susceptibility of the female sex (1). Women are at least tenfold more likely to develop SLE, for instance (2). The female predominance is also true of most animal models of autoimmunity, with a few notable exceptions. Efforts to understand the female tendency to develop autoimmune disease have not been entirely successful, but hormonal influences play a major role, and endocrinologic abnormalities have been described (3,4).

A third feature of autoimmune disease is called overlap, the finding in individual patients of features of multiple systemic autoimmune disease (5). This leads to taxonomic confusion; for example, some patients have an autoimmune disease sometimes termed *mixed connective tissue disease,* which has features of SLE, scleroderma, and polymyositis (6).

It seems paradoxical that humans and animals with systemic autoimmune disease, despite their high immunoglobulin and autoantibody levels, respond poorly when immunized with exogenous antigens, as if their immune systems were preoccupied with responses to self antigens (7). Cell-mediated immunity is particularly impaired (8), possibly reflecting the lymphocytopenia characteristic of SLE but also seen in other disorders (9). This immunosuppression may be further exacerbated by medical efforts to suppress autoantibody formation; infection due to immunosuppression is a regrettably common feature in patients suffering from systemic autoimmune disease (10).

HISTORY

To early immunologists, the notion that autoantibodies or self-reactive cellular immunity could ever occur met with considerable resistance. It had been observed, for example, that immunization of animals with mixtures of self and foreign erythrocytes elicited antibody only against blood from other individuals. Ehrlich and others proposed that the consequences of the formation of self antibodies were so severe (*horror autotoxicus*) that the immune system stringently prohibited its occurrence (11). Although investigators as early as Donath observed clear evidence of anti-self agglutinins, acceptance of the concept that autoantibodies could cause immune injury came from the convincing experiments of Harrington in human idiopathic thrombocytopenic purpura (ITP) (12), in which the profoundly low platelet counts of the ITP patients were reproduced in the investigator and his colleagues by transfer of patient serum; and from the pioneering work of Rose and Witebsky in rabbit experimental thyroiditis (13). An important intellectual figure

of the era was F.M. Burnet, who extended the clonal selection theory to postulate the elimination of self-reactive antibody-producing cells (14).

NONPATHOLOGIC SYSTEMIC AUTOIMMUNITY

Autoimmune disease must be distinguished from the many instances of nonpathologic self-recognition by the immune system. These include the ready isolation of self class II reactive T-lymphocytes (15) and the existence in normal individuals of low levels of autoantibodies to certain self proteins (16). The use of binding assays like ELISA further complicates the definition of autoantibodies, as low-titer, low-affinity autoantibodies can be readily detected in the sera of normal individuals using almost any assay system of sufficient sensitivity. Even when threshold values are set to exclude low-titer positives, antinuclear antibodies and rheumatoid factor (RF) are seen in small but significant numbers of normal humans (17) and become more prevalent among the aged and among hospitalized patients (18).

Autoantibodies to some self proteins may serve important physiologic functions. This has been best shown for RF, antibody against IgG. RF is mainly IgM, and a substantial fraction of IgM-bearing lymphocytes express this specificity (19). RF levels rise promptly after immunization with foreign antigens (20,21), and the antibody is commonly observed in the serum of patients with chronic infections (22). RF probably serves to eliminate immune complexes; its affinity for monomeric IgG is low, yet is much higher for the multimeric IgG that exists in complexes. The binding of RF to complexes very likely expedites their removal from the circulation via the mononuclear phagocyte system.

RF-bearing B cells may also serve an important function in presenting foreign antigens, by virtue of their binding of antigen–antibody complexes (23). Mice expressing a human RF transgene produce little circulating RF; their RF-producing B cells are found in primary B-cell follicles and the mantle zone of secondary splenic follicles (24). Spleen cells from these RF transgenic mice present human IgG antitetanus toxoid immune complexes with high efficiency. The resulting wave of T-cell help may serve to amplify the immune response, and its subsequent downregulation may be related to deletion of many of the RF-bearing cells (25).

As depicted in Fig. 1, low-affinity IgM antibodies against other self antigens have been observed in unimmunized animals (16,26–30). The function of these specificities is uncertain and may include shaping of the repertoire against exogenous antigens. The fetal repertoire is rich in such antibodies, which are derived from a limited set of VH and VL genes with limited somatic mutation (31).

The B1 subset of B-lymphocytes, which in rodents is concentrated in the peritoneal cavity, may have as its primary function the production of IgM autoantibodies such as RF (32). In mice, B1 cells may be responsible for production of antierythrocyte autoantibodies (33), but they are not the source of antichromatin antibodies or RF in the *lpr* model (34), nor do they produce such antibodies in GVHD (35). In SLE, both B1 and B2 cells secrete anti-DNA, but high-affinity autoantibody is derived from the B2 cells (36).

Autoantibodies to idiotypes are another form of nonpathogenic humoral autoimmunity. Antiidiotypes arise after immunization and have been shown to mediate both negative and positive feedback of humoral responses, in some systems, via regulatory T cells (37–39).
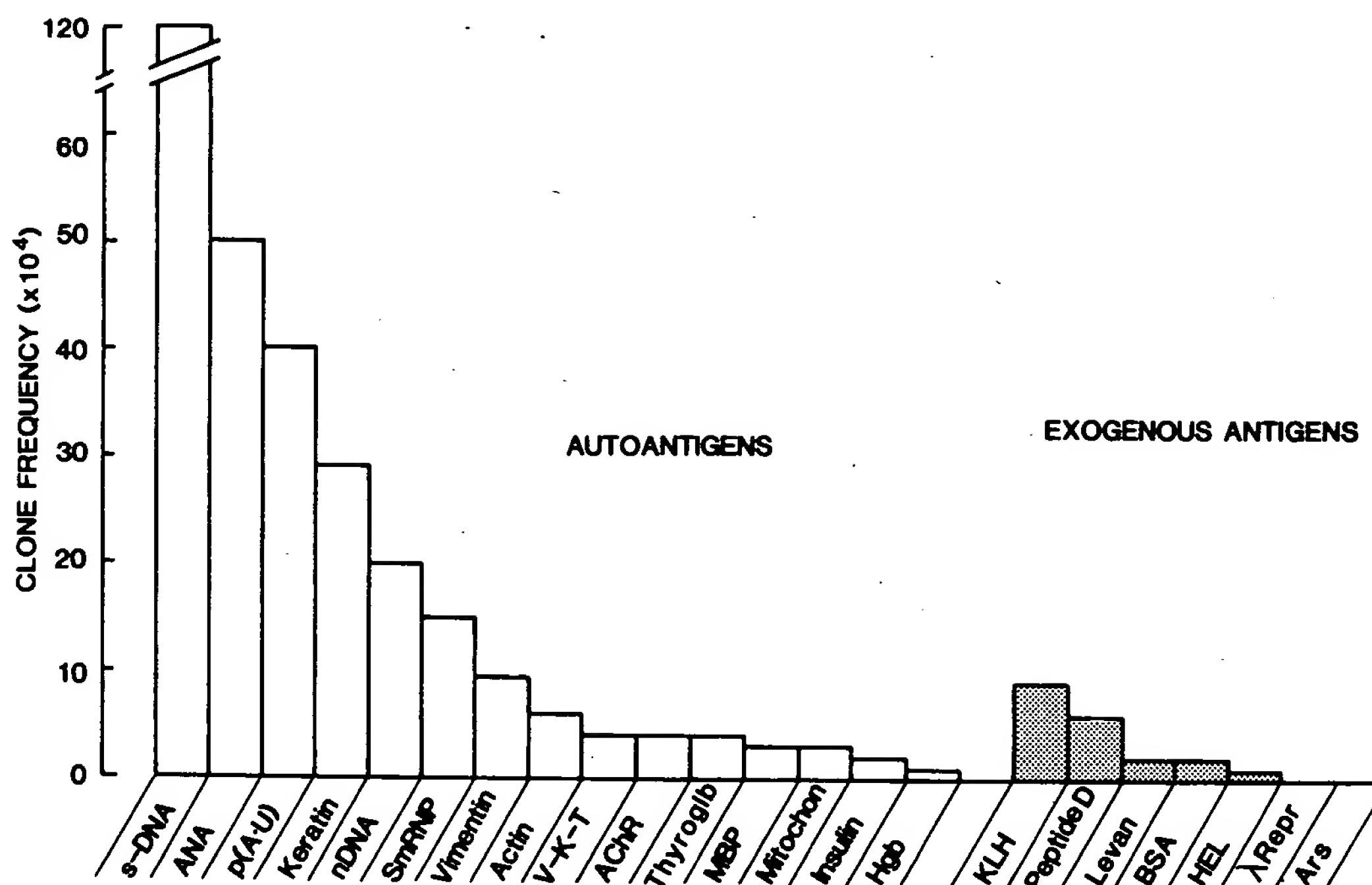
FIG. 1. The natural autoantibody repertoire in normal mice. Antibodies produced by 11,800 hybridomas prepared from splenic B cells of unimmunized 6-week-old A/J mice were screened for reactivity against a panel of autoantigens and foreign antigens. Note the high frequency of antibodies against nuclear and cytoskeletal antigens. (From Souroujon M, White-Scharff ME, Andre-Schwartz J, Gefter ML, Schwartz RS. Preferential autoantibody reactivity of the preimmune B cell repertoire in normal mice. *J Immunol* 1988;140:4173–4179, with permission.)

TOLERANCE AND AUTOIMMUNE DISEASE

The establishment and maintenance of immunologic tolerance is a key feature of the immune system, and is fully discussed elsewhere. The occurrence of autoimmunity may reflect the imperfect nature of the tolerance generated in the developing T- and B-cell repertoires. Very likely, peripheral tolerance mechanisms are required to prevent the emergence of autoimmunity in adult life. No autoimmune disorders have thus far been shown to involve deficits in intrathymic tolerance, and autoimmune diseases typically do not occur in the neonatal period.

Data show that intrathymic tolerance is of potential importance in establishing tolerance to nuclear antigens (40). B-cell tolerance to protein antigens may be abnormal in certain autoimmune disease models (41,42).

It is typical of systemic autoimmune disease, that, rather than a global loss of tolerance, there is a selective autoimmune response directed primarily against intracellular autoantigens, and especially against components of the nucleus (43).

Role of T cells in Systemic Autoimmune Disease

It is not difficult to find evidence in normals of T-cell autoreactivity to class II major histocompatibility complex (MHC) antigens (44). The degree to which this represents autoreactivity to self peptides, compared with reactivity to the class II MHC molecule itself, is difficult to determine. Perhaps contrary to expectation, self-Ia–reactive T cells are less abundant in human and

murine systemic autoimmunity (45), and this defect may vary with disease activity. Cloned autoreactive T cells, on the other hand, are associated with induction of disease in some models. They elicit lesions typical of the inflammatory skin disease lichen planus (46) and are present among the hyperproliferative T cells found in mice expressing the *lpr* Fas mutant gene (47). Whether such self-reactive cells are involved in providing help for autoantibody production is unknown.

Besides any role as helpers, T cells may provoke cellular injury in systemic autoimmunity. In chronic GVHD, CD4- and CD8-bearing T cells cause inflammatory infiltrates in skin, intestine, and elsewhere (48). There is evidence that T cells in systemic lupus are spontaneously activated, as judged by increased expression of activation antigens (49,50). T-lymphocytes are found in inflammatory skin lesions (51) and may be responsible for some of the other nonrenal manifestations of the illness (52,53). For the most part, however, autoimmunity mediated directly by T cells seems to be more characteristic of organ-specific autoimmune disease such as experimental allergic encephalomyelitis (EAE) than it is of systemic autoimmune disease.

Systemic autoimmunity is thus usually mostly a problem of B-cell production of autoantibodies, yet the contribution of T cells to these autoantibody responses has been difficult to define. Thymectomy in SLE may lead to exacerbation or remission of disease (54). Human immunodeficiency virus (HIV) infection of SLE patients, with its depletion of CD4-bearing T cells, results in a remission in SLE activity (55,56), supporting a role for a continuing source of T-cell help for SLE autoantibodies.

Some properties of systemic autoimmune disease strongly suggest the involvement of helper T-lymphocytes. Autoantibody responses are high-affinity IgG responses (57), which appear to have undergone affinity maturation, a process that requires T cells. The protein antigens to which many antinuclear antigens are directed presumably require T-lymphocyte help, as they do not possess the repeating determinants characteristic of most T-independent antigens. Some of the treatments for SLE appear to act primarily at the T cell, e.g., cyclosporine A and cyclophosphamide.

Even in patients with high-titer autoantibodies, T-cell proliferation to nuclear autoantigens has been difficult to demonstrate. There are several well-documented examples, however: T cells from SLE patients respond to a recombinant form of the SLE-associated ribosomal protein P2 autoantigen. Under the same conditions, responses to tetanus toxoid are poor, suggesting that the autoantigen-specific response occurs despite generalized T-cell dysfunction (58). In another report, CD4$^+$ T cells against a recombinant snRNP protein were found in high frequency (1/4,000 →~ 1/25,000) but were not seen in normal subjects (59). In contrast, snRNP A protein-reactive T cells could be isolated both in normal individuals and in patients (60).

Some of the most extensive work on specificity of T helper cells in systemic autoimmunity comes from analysis of clones of SLE T cells which provide help for anti-DNA. These cells have charged motifs in the T-cell receptor (TCR) CDR3s, presumably promoting binding to peptides derived from charged DNA-binding nucleosomal proteins [high-mobility group (HMG) and histones]. Anti-DNA–specific B cells probably bind to the DNA, bringing along the attached proteins, and internalize and process them for presentation to CD4$^+$ T cells (61). It has been reported that at least some SLE T cells that provide help for antinuclear antibody production lack both CD4 and CD8 and express αβ TCRs (62).

SLE mouse models have allowed in vivo experiments to define the role of T cells. Treatment of NZB/NZW mice with anti-Thy 1 or anti-CD4 prevents autoantibody production and renal disease (63). Thymectomy of this strain, on the other hand, exacerbates autoimmunity, reflecting complex T-cell interactions early in life. In the lpr model (64), thymectomy prevents disease if done within 72 hours of birth (65), and antibody depletion of T cells prevents both autoantibodies and lymphoid hyperplasia (66).

Even in these defined genetic models, the precise role of T cells and the amount of nonspecific versus specific help for autoantibodies has been elusive. The T-cell repertoire of NZB/NZW mice, despite its content of autoantigen-specific T cells, shows polyclonal and not oligoclonal T-cell activation (67). In MRL/lpr mice, disease fails to develop in animals in which a source of normal T cells is provided, but in which lpr T cells have been depleted, indicating that the T cells provide more than just a passive source of cytokines or nonspecific help and that they participate actively as helpers for autoantibody-producing B cells (68). The extreme restriction of the TCR repertoire imposed by expression of a TCR β transgene has been reported to result in lower autoantibody levels and increased survival in MRL/lpr mice (69), suggesting again that autoantigen-specific T-cell help is required for autoantibody production.

Because the transgenic studies could be confounded by the ability of mice to express endogenous α or β chains, MRL/lpr mice transgenic for both the α/β chains of a pigeon cytochrome C hybridoma have been constructed by breeding the TCR transgenes onto TCR α and β knock-out mice (70). These animals expressed only the transgenic TCR, yet hypergammaglobulinemia and autoantibodies to IgG, DNA, and snRNPs developed despite the lack of autoantigen-specific T-cell help. Lymphadenopathy, renal, salivary, and cutaneous disease were absent, suggesting that more specific T-cell help was required for these manifestations. These studies indicate that both antigen-specific and antigen-nonspecific T-cell help are required for full development of the MRL/lpr SLE syndrome. In this regard, chimera studies, in which lpr mice have been constructed using congenic donors in which T-B interactions could be analyzed, have shown that the T help required for autoantibody production is MHC-restricted; in other words, autoreactive T cells must share class II MHC determinants with autoreactive B cells in order for autoantibody production to occur (71).

The role of γδ T cells has also been evaluated in MRL/lpr mice by comparing disease manifestations and autoimmunity in mice lacking γδ T cells (72). In the absence of the latter, mice developed a more severe autoimmune syndrome, suggesting a regulatory role for γδ T cells. In the converse situation, mice lacking αβ T cells had only an attenuated SLE syndrome, implying that γδ T cells were capable of providing significantly less help for autoantibody production than were αβ T cells.

Autoantigen-reactive T cells have been studied in murine models. For MRL mice, which are prone to develop antibodies to the snRNP complex, snRNP-reactive T cells can be demonstrated in draining lymph nodes after immunization with purified snRNPs (73). While normal mice can generate T cells reactive to foreign snRNP, only MRL mice and mice expressing certain MHC alleles can recognize snRNP of murine origin (74). The ability of normal mice to recruit T cells reactive to self antigens after immunization with foreign nuclear antigen may reflect epitope spreading. This process entails the recruitment of T cells reactive to self peptides as a result of the presentation of self antigen by B cells cross-reactive with self proteins.

T cells reactive to overlapping core histone peptides have been described in SLE-prone SWR×NZB F1 mice (75). These antigenic determinants are apparently protected in intact chromatin, as responses to whole histone are not measurable. Interestingly, these T-cell antigenic regions of histones overlap with determinants recognized by antihistone autoantibodies. T-cell help for autoantibodies may also be mediated through T cells with specificity for the variable regions of autoantibody molecules.

NZB/NZW mice develop T cells that recognize peptides corresponding to the variable regions of anti-DNA antibodies (76). Presumably there is presentation to T cells of peptides derived from the processing of self immunoglobulin by B cells. The resulting helper T cells can provide autoantibody-specific help, and interference with their action has been reported to ameliorate autoimmune disease.

CD40 ligand (CD40L) may play a critical role in regulating autoantibody production in SLE. Expression of this T-cell activation-related molecule is increased in SLE patients, especially those with active disease, and also appears on some SLE B-lymphocytes (77). The latter observation may account for a relative T-independence of some SLE antibody formation. Treatment of NZB×SWR F1 mice with antibody to CD40L prevents autoimmune disease (78). MRL/lpr mice that are genetically deficient in CD40L, in contrast, develop autoantibodies to nuclear antigen, but these are skewed toward the IgM isotype, suggesting impairment of class switching (79). Renal disease appears to be diminished in such mice.

Role of Antigen

Unlike immune responses arising from deliberate immunization, it is not obvious that autoimmunity is initiated or perpetuated by

self antigen. Other mechanisms can be conceived, and some have been seriously put forth. For instance, the diffuse activation of B cells by lipopolysaccharide (LPS) leads to limited systemic autoimmunity (chiefly IgM antibodies to DNA and RF) and may be a good model for the autoimmunity that accompanies certain infections [e.g., Epstein-Barr virus (EBV) and mycoplasma (80)]. It is also possible that aberrations in the web of idiotypes and antiidiotypes could result in autoimmunity without the need for autoantigen as immunogen. Yet considerable evidence supports the view that self antigens themselves act as immunogens for autoantibody responses

Autoimmunity against nuclear protein complexes such as the snRNP spliceosome is directed against multiple components of the autoantigen, as might be expected from an immune response to the intact particle (81). Analysis of the fine specificity of these responses has revealed a further complexity consistent with what might be expected from a high-affinity, antigen-driven response (82,83). Immunization with nuclear antigens, in some cases, may result in autoantibody formation and disease (84), although antigens need to be repeatedly administered in adjuvant, and the complexity of the resulting autoantibody response is usually much reduced.

Immunization of rabbits and mice with small peptide fragments of certain autoantigens has been reported to result in antigen not only to the immunogenic epitope, but also to other epitopes on the same antigen and even to autoantibodies to other nuclear antigens and clinical evidence of SLE (85). This may reflect epitope spreading (i.e., the recruitment of T cells reactive to additional epitopes on the autoantigen). As tolerance usually does not extend to all such "cryptic" epitopes, a mechanism that might be capable of enlisting progressively more autoreactive T cells might amplify any initial breakage of tolerance. The impetus for such responses might come from immunization with autoantigens from another species, which could elicit T-cell help against *bona fide* foreign determinants, along with the generation of antibody against the foreign antigen (86). B cells expressing antibody cross-reactive with self determinants could then selectively take up autoantigens, process them, and express autoantigenic peptides, including cryptic epitopes. The physical association of many autoantigens, such as Ro and La (87), or the many components of the snRNP complex, could lead to further diversification of an autoimmune response initiated by the breaking of tolerance to only a single autoantigen. For the La nuclear antigens, a hierarchy of immunogenic cryptic epitopes with differing potential for driving a full autoimmune response has been identified using peptide fragments of the intact antigen (88).

Immunization of animals with mammalian DNA generally does not lead to autoantibody unless the DNA is complexed to a cationic protein such as methylated bovine serum albumin (89). DNA that has been damaged by ultraviolet (UV) irradiation or by reactive oxygen species is much more immunogenic than unaltered DNA, which may be relevant to UV-induced SLE exacerbations (90). Much interest has focused on the potential of bacterial DNA to activate B cells and provoke autoimmune responses through CpG motifs not found in mammalian DNA (91). Exposure to bacterial DNA also accelerates genetically predetermined autoimmune disease in NZB/NZW mice (92). Although it is possible that microbial DNA is an immunogen in SLE, the bulk of the small amount of circulating DNA in SLE has been shown to be of human origin and mostly in the form of small complexes bound to histone (93,94).

If nuclear antigens serve as immunogens, how do they interact with the immune system? The most likely answer is that they are released from senescent cells, or are presented on the surface of phagocytic cells that have ingested such debris. Cells undergoing apoptosis have been shown to express several important SLE nuclear antigens (95) and may serve as an important source of autoimmunogen. It seems doubtful that the apoptotic cell can serve as a competent antigen-presenting cell (APC) for these molecules; rather, it seems more likely that specialized APCs would serve to present these apoptosis-related nuclear antigens, perhaps the same cells that so avidly phagocytose apoptotic cells.

The elution of peptides from both class I and class II MHC molecules provides further reason to believe that nuclear autoantigens are presented to the immune system. Both in rodents and in humans, MHC molecules have been found to have peptides derived from such nuclear antigens as histone on their cell surfaces, presumably through the processing of nuclear debris (96). It is also possible that these peptides are derived from autoantigens processed from within normal antigen-processing cells using a class II pathway, although examples of such "inside out" class II processing are uncommon (97).

Regulatory T-Cell Abnormalities

Much evidence suggests that T cells can exert a controlling influence on the generation of autoantibodies and on the regulation of autoimmunity (98). Thymectomy of normal animals, in some systems, results in autoimmunity, both systemic and organ-specific (99). Nude mice develop autoantibodies and immune complex renal disease, and the process can be reversed by adoptive transfer of T cells (100,101). These studies imply that regulatory T cells may control antinuclear antibody production. In SLE, there are multiple reports of *in vitro* abnormalities of regulatory T-cell function both in animals and in humans (102). Much of the suppressor-cell literature of the 1970s is now better regarded in light of the current concepts of classification of both helper and cytotoxic cells into T helper 1 (Th1), Th2, TC1, and TC2 subsets based on their cytokine phenotype (103). It is likely that some of the observed phenomena represent the action of cytokines derived from these T-helper subsets, for example, interferon-γ (IFN-γ), interleukin-10 (IL-10), and IL-4, which have potent effects on the magnitude and character of humoral immune responses.

An important example of perturbation of regulatory T cells is the autoimmune and GVHD-like syndrome induced by cyclosporine treatment of irradiated rats reconstituted with autologous marrow (104). While animals become immunocompetent, the T-cell imbalance brought on by the protocol leads to autoimmune disease.

Cytokines in Systemic Autoimmune Disease

A multiplicity of cytokine abnormalities have been associated with systemic autoimmune diseases and models. Some occur late in illness and are probably not causal, while others may be actively involved in regulation and dysregulation of immune responses. In general, IL-2 levels and the expression of IL-2 receptors are diminished both in human and murine SLE (105) and in several related autoimmune disorders (105). Circulating IL-2 receptors may be increased, however, in parallel with other circulating receptors (106), although assays for these receptors are difficult. Efforts to characterize SLE as a Th2 or Th1 disease based on the phenotype of helper cells have met with difficulty, but IL-10 seems to be increased in human and murine SLE, along with IL-6. The ratio of

IL-10 to IFN-γ–secreting cells in SLE peripheral blood is increased, implying a predominance of Th2 cells in the circulation (107). Supporting the importance of Th2 cells in promoting systemic autoimmunity is the observation that some IL-4 transgenic mice develop SLE-like antinuclear antibodies, hemolytic anemia, and immune-mediated renal disease (108).

There have been several published surveys of cytokine production in murine SLE models. For chronic GVHD, a Th2 profile has been observed (109). For NZB/NZW and MRL/lpr, however, a complex pattern not fitting either Th1 or Th2 exists, with increases in IL-6, IL-4, and IL-10 (110). Tumor necrosis factor-α (TNF-α) may also be increased, and evidence has been published that allelic polymorphisms at this locus predispose to SLE (111,112).

APOPTOSIS ABNORMALITIES IN SYSTEMIC AUTOIMMUNE DISEASE

The realization that the autoimmune and lymphoproliferative syndrome of lpr and gld mice was due to mutations in the Fas apoptosis receptor and its ligand led to great interest in the possibility that impairment of apoptosis might be responsible for other autoimmune diseases. Because multiple pathways of apoptosis exist, many possibilities exist for potential lesions. In human SLE, spontaneous lymphocyte apoptosis appears increased (113). Expression of bcl-2 appears to be elevated (114), particularly in T cells (115). Fas expression is elevated (116), contrary to what might be expected from murine studies, and apoptosis through the Fas molecule is apparently intact (117). The status of Fas ligand (FasL) expression and function is not yet clear for SLE, and conflicting data have been presented. It is of great interest, however, that an SLE patient with a mutant FasL has been identified (118).

The Canale-Smith syndrome, also known as autoimmune and lymphoproliferative syndrome (ALPS), is a rare illness resulting in lymphoid enlargement and immune cytopenias (119,120). In a number of kindreds, the disorder results from a dominant nonfunctional Fas molecule. Like lpr and gld mice, children develop "double-negative" T cells and hypergammaglobulinemia. Unlike the murine mutations, however, affected patients rarely develop antinuclear antibodies or lupus-like renal pathology. It is significant that, in the few long-term observations of such patients, an increased susceptibility to malignancy has been noted.

The apoptosis resistance imparted by the mutant Fas molecule in lpr mice has been intensively studied. Thymic selection, as reflected by deletion of I-E and mammary tumor virus–reactive T cells, is normal in lpr mice. Nevertheless, there is evidence for abnormal thymic T-cell development in lpr mice, both in intact and in transgenic mice. The intense Fas expression on thymic T cells (121), however, makes it paradoxical that only subtle thymic selection defects are apparent in lpr and gld mice.

If thymic deletion is intact, how does the Fas apoptosis defect lead to autoimmunity? At least part of the answer is that peripheral T-cell tolerance is strongly dependent on the Fas/FasL system, as deduced from studies of tolerance in lpr mice transgenic for a pigeon cytochrome-C TCR (122). The imposition of the Fas defect on such transgenic mice leads to their inability to achieve tolerance in spleen and lymph nodes. Additional support for the idea that it is in the periphery that Fas/FasL contribute to tolerance comes from the observation that activation-induced cell death is abnormal in peripheral lpr T cells (123). The Fas/FasL interaction appears to act as an important mechanism to eliminate errant autoreactive postthymic T cells. The delayed development of autoimmunity in lpr mice probably reflects the gradual appearance and clonal expansion of such autoreactive T cells.

Chimeric (124) and tetraparental (125) experiments in which lpr T or B cells coexist with cells of normal origin have shown that B cells must also express the Fas defect in order for autoimmunity to occur; there is direct evidence for defective B-cell apoptosis in lpr and gld mice (126). In vivo studies of tolerance using transgenic self-reactive antibodies have shown surprisingly little difference between lpr and normal mice. In the HEL-anti-HEL system, most B6/lpr mice maintain tolerance through early life. A significant minority, however, break through and generate autoantibodies at 5 months and beyond (42). These findings imply that other mechanisms can substitute effectively for the Fas/FasL system for maintenance of tolerance. Parallel results are reported for mice with an anti–H-2^k transgene: in a conventional facility, most mice maintain tolerance (127). When housed in a specific pathogen-free colony, however, tolerance is intact, suggesting an important role for microbial influences (see above).

Of potential importance regarding the relationship of apoptosis and autoantibody formation are data showing that SLE-related nuclear autoantigens such as Ro and La appear in blebs on the surface of apoptotic cells (95). These and other observations that SLE serum contains antibodies to proteins expressed in apoptotic cells (108) raise the possibility that the process of apoptosis may serve to expose autoantigens to the afferent limb of the immune system. Impairments of apoptosis, or of the process of rapid phagocytosis and disposition of apoptotic bodies, might serve to present autoantigens to the immune system and provoke T- and B-cell autoreactivity.

Among the other commonly used autoimmune mouse models, apoptosis resistance for NZB, NZB/NZW, and BXSB B cells has been reported and may contribute to the expression of disease in these models (128).

ENVIRONMENTAL INFLUENCES ON SYSTEMIC AUTOIMMUNITY

Systemic autoimmune disease may be provoked or exacerbated by a variety of environmental agents, including diet, drugs, infections, and toxins (129). UV-B radiation can provoke flares of SLE, and it is apparent that inflammatory skin lesions are usually limited to light-exposed areas.

The ingestion of certain drugs is clearly linked to development of an SLE-like syndrome (130,131). Unlike spontaneous SLE, renal and central nervous system involvement is rare, and the syndrome resolves after discontinuing the drug. Procainamide, used extensively for treatment of ventricular arrhythmias, is the best-studied agent provoking drug-induced SLE, but hydralazine, chlorpromazine, diphenylhydantoin, and many other drugs can also cause the SLE-like syndrome, characterized mainly by pleuropericarditis, arthritis, pulmonary infiltrates, and fever. Only about 10% of patients given procainamide develop clinically evident disease, but fluorescent antinuclear antibodies appear in the vast majority of patients taking the drug for prolonged periods. Antibodies are directed mostly against histones, and a distinct specificity and isotype pattern have been reported (132,133). No relationship to procainamide acetylator frequency governs SLE development. Efforts to reproduce the syndrome in animals have been largely unsuc-

cessful. It has been proposed that procainamide exerts its action by hypomethylation of DNA, with consequent overexpression of LFA-1 on T-lymphocytes, leading to enhanced autoreactive T-cell help (134).

The contribution of infectious agents to systemic autoimmunity remains an active area of investigation. It is clear that systemic autoimmunity can arise as an immediate consequence of infection with EBV and mycoplasma, and probably other viral infections (135,136). Antinuclear antibodies arising after infectious mononucleosis are short-lived and probably are harmless. Systemic autoimmunity may also arise during the course of severe microbial infections, such as endocarditis and osteomyelitis. Occasionally, skin and kidney lesions are seen, probably representing deposits of immune complexes, possibly associated with RF(137).

Vasculitis, discussed in detail later, accompanies meningococcal, rickettsial, spirochetal, and many other bacterial infections. Systemic autoimmunity is also a sometime feature of HIV infection and may reflect imbalance of helper-cell subsets (138). Various bacterial superantigens have been implicated in autoimmune phenomena, including vasculitis, associated with infections (139). Kawasaki disease, caused by an unknown agent, causes a serious vasculitis and alterations in TCR V_β phenotype, suggesting the role of a superantigen (140).

The influence of infection on the development of SLE is unclear. NZB mice that are maintained germ-free still develop antierythrocyte autoantibodies (141); however, NZB mice in a germ-free environment developed lower levels of IgG and antinuclear antibodies and less renal disease. Immunization of NZB/NZW mice with bacterial DNA accelerates development of renal disease (92), and pristane-treated mice that are maintained in a conventional colony have a higher prevalence of autoantibodies and renal disease than do mice maintained in a pathogen-free environment. MRL/*lpr* mice, in contrast, develop similar levels of autoantibodies when raised in germ-free compared with conventional environments.

Certain toxins are capable of inducing systemic autoimmune disease. Mercuric chloride is the best-studied heavy metal associated with autoimmunity. Animals given $HgCl_2$ develop antinuclear antibodies and immune-complex nephritis. T cells are required, and background genes are important determinants of autoantibody specificity (117,142,143).

Systemic sclerosis and related fibrotic diseases believed to be of autoimmune origin may rarely be provoked by toxins. Workers exposed to polyvinyl chloride are at risk for a scleroderma-like syndrome (144), and an inflammatory and fibrotic scleroderma-like illness has been linked to the ingestion of rapeseed oil (145). An eosinophilic infiltrative disease is caused by a contaminant of L-tryptophan preparations (146). An area of great controversy has been the relationship between silicone breast implants and the development of scleroderma or other rheumatic diseases. Several studies have failed to find a true association (147,148), despite anecdotal reports.

GENETICS OF SYSTEMIC AUTOIMMUNE DISEASE

Susceptibility to SLE is strongly influenced by genetics. In studies of identical twins with SLE, the concordance rate has been reported to be between 28% and 57% (149,150). Multiple genes are involved in determining SLE susceptibility; even in inbred mouse models, the genetics is complex, with as many as 12 genes

contributing (151). Furthermore, genes that alone do not cause disease may interact with other genes to result in disease. For instance, neither the NZB nor the NZW parent strains develop renal disease or antinative DNA antibodies, yet the F1 hybrid resulting from their crossing develops severe SLE-like renal disease and antinative DNA. The most important NZW genetic contribution to murine SLE is linked to the MHC, probably MHC class II genes. NZB contributes a chromosome 4–linked gene that is most important for nephritis, but at least seven other genes have been reported to contribute. Surprisingly, the chromosome 4 gene determining nephritis susceptibility does not affect the levels of anti-DNA, anti-histone, and antichromatin (152).

A study using microsatellite markers to analyze sib pairs with SLE defined a region of chromosome 1 linked to disease susceptibility (153). This region may be syntenic to the region of mouse chromosome 1 previously shown to encode renal disease and mortality in NZB mice. While the region encompassed by these studies is large and remains to be defined further, candidate genes include those for Fc receptor gamma 2 and 3; previous human epidemiologic studies have shown linkage in blacks of SLE nephritis to Fc receptor alleles (154).

Genetic deficiencies of complement result in increased risk of SLE (155). C2-deficient individuals are at greatly increased risk of developing SLE, as are those with inherited deficiencies of C8 and C5; the inheritance of a C4 null allele is also a risk factor (156). MHC influences on SLE susceptibility have been harder to define than for RA, insulin-dependent diabetes mellitis (IDDM), and other organ-specific autoimmune diseases (157). For North American blacks, one study found no overall DR association, both associations with subgroups divided according to clinical findings (158). For developing the disease-related autoantibodies anti-Ro and anti-La, susceptibility appears to be linked both to DR and to DQ genes (159).

NATURE OF THE AUTOANTIBODIES IN SYSTEMIC AUTOIMMUNE DISEASE

With some notable exceptions, the autoantibodies characteristic of systemic autoimmune disease are high-titer IgG antibodies (160). The genetic basis of autoantibodies has been best studied in mice, where hybridomas have been useful for sequence analysis (161). Several insights have emerged concerning antinuclear antibodies in NZB/NZW and MRL/*lpr* mice; within a single mouse, anti-DNA and other autoantibodies recovered from hybridomas tend to be clonally related (162). For anti-DNA and anti-Sm, there is evidence of extensive somatic mutation when sequences are compared to germline, and clonal lineages can be deduced (163). Many clones show dual reactivity, implying a common ancestry for at least part of these specificities (164). The binding site of antinuclear autoantibodies is dictated neither by the VH nor the VL hypervariable regions, but usually by a combination of both (165). Anti-DNA antibodies may arise from point mutations in the hypervariable regions of antibodies to exogenous antigens (166). For the S107 response to pneumococcal polysaccharide, a pathogenic anti-DNA antibody can arise from just such a mutation (167). It is not clear how widespread is this mechanism of diversion of normal immune responses to autoimmune responses.

Enough hybridoma autoantibodies from autoimmune mice have now been sequenced that generalizations can be made about VH and VL gene use. Although it appeared in early work that there was

preferential use of 3' VH genes, there are, at best, only modest degrees of bias, and it appears that the VH558 group is the most commonly used gene family, as is the case for antibodies to exogenous antigens (168).

Extensive epitope-mapping studies have been undertaken for many antinuclear antibodies. In most cases, it appears that the antibodies recognize multiple conformationally dependent, often discontinuous, epitopes of nuclear proteins (169,170). There is a predilection for binding to the active site of nuclear proteins; thus, the function of certain enzymes and other autoantigens may be inhibited by autoantibody-containing sera. Antibodies to RNA are often found together with antibodies to the protein components of the snRNP particle, as well in sera containing antibody to other RNA-binding proteins (171). Autoantibodies in systemic autoimmune disease usually bind with greater avidity to antigen derived from the same species, emphasizing their derivation through affinity maturation and their probable origin from immunization with self proteins.

Isotype switching from IgM to IgG has been observed for some but not all autoantibodies. Anti DNA antibodies in NZB/NZW mice undergo this process (172), as do certain serial samples of human sera. MRL/lpr anti-Sm sera, however, either switch too rapidly for the change to be measured, or are IgG at the outset (173). It is of interest that autoantibodies in human and murine SLE are mostly of the highly T-dependent IgG (human IgG1, mouse IgGa and IgG2a) subclasses, probably reflecting their T-cell dependence (174,175).

It is not understood why certain protein antigens are the targets of autoantibody formation in systemic autoimmune disease. Autoantigens are nearly always intracellular or cell surface proteins (RF is a prominent exception), and nuclear antigens account for most of the autoantigenic targets. Just why certain nuclear proteins are chosen is particularly obscure. It is not a question of abundance; for instance, the Ro and La proteins are far from the most abundant nuclear proteins, yet are characteristic SLE autoantigens (176).

Attention has been focused on certain aspects of nuclear autoantigens. Individuals with autoimmune diseases frequently have autoantibodies to multiple components of subcellular particles, such as ribosomal proteins, nucleoli, or snRNPs (177). This is suggestive of immunization by the particle itself. Autoantibodies also tend to be directed against nuclear antigens, which are present in greater amounts in cells undergoing proliferation. For instance, proliferating-cell nuclear antigen (PCNA), the centromeral proteins, and the nuclear mitotic apparatus protein NuMa are present in greatly increased concentrations during S and G2 phases of the cell cycle (178). Perhaps nuclear antigens are more available as immunogens at such times.

Antinuclear antibody levels can be quite high. In exceptional patients, 30% or more of the total antibody repertoire can be directed against a single specificity (179). Certain autoantibody levels fluctuate with disease activity (antinative DNA is the best known example), but in the more usual case, antibody levels are fairly constant over time.
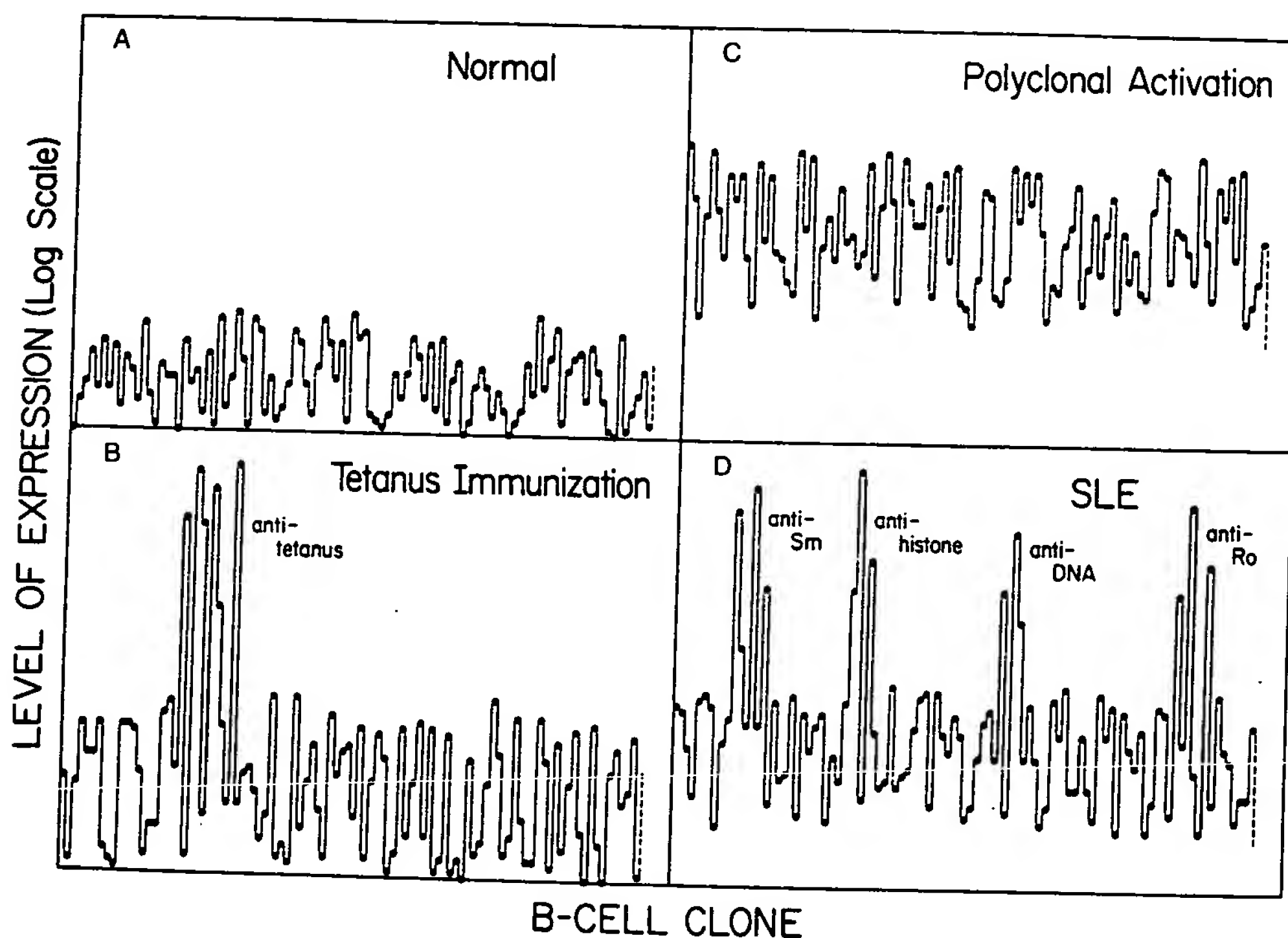
FIG. 2. Nature of autoantibody production in SLE. **Panel A:** Antibody arising from multiple B-cell clones in a normal individual. **Panel B:** Tetanus toxoid immunization is shown to provoke a group of tetanus-specific B-cell clones, along with a modest degree of polyclonal activation. **Panel C:** The effect of diffuse polyclonal activation resulting from exposure to bacterial lipopolysaccharide or other polyclonal B-cell activator. In contrast, **panel D** illustrates the usual situation in SLE and other systemic autoimmune diseases, namely, a background of polyclonal B-cell activation together with large amounts of autoantibody arising from a discrete number of clones of defined specificity. (Reprinted from Eisenberg RA, Cohen PL. Mechanisms of autoantibody production in systemic lupus erythematosus. Clin Asp Autoimmun 1988;2:11, with permission.)

TABLE 1. *Autoantibodies to nuclear proteins in systemic autoimmune disease*

Specificity	Antigen recognized	Disease association
Sm	U1,U2, U4–6 snRNPs	SLE
RNP	U1 snRNP	SLE, MCTD
Ro (SS-A)	60-KdtRNA-binding protein	SLE, Sjogren's syndrome
La (SS-B)	50-KdaRNA-binding protein	SLE, Sjögren's syndrome
Histone	H1, H2a, H2b, H3 (native)	SLE
Jo-1	Histidyl tRNA synthetase	Myositis
Scl-70	DNA topoisomerase I	Scleroderma
PCNA (cyclin)	DNA polymerase delta	SLE
Alu	Signal recogn. particle	SLE, myositis
PL-7	Threonyl tRNA synthetase	Myositis
tRNA-1	Alanyl tRNA synthetase	Myositis, SLE, JRA
RNA polymerase I		Scleroderma
DNA (native)	Double-stranded DNA	SLE
DNA (denatured)	Single-stranded DNA	SLE, RA, inflammation
Centromere	CENP A, B, C	Raynaud's syndrome, CREST

Autoantibodies in SLE and SLE models occur in the midst of diffuse polyclonal B-cell activation. Antibodies to haptens, such as DNP, and to viral antigens are increased on the order of five- to tenfold (180,181). In contrast, the levels of specific autoantibodies, such as antibodies to snRNP, or to Ro and La, are elevated far out of proportion to the polyclonal B-cell activation, and are not uncommonly thousands- or millions-fold greater than the weak binding that might be found in normal control serum (Fig. 2).

Certain SLE serologic specificities are seen in a variety of autoimmune and inflammatory diseases, and do not connote diagnostic specificity. Examples include antihistone and anti-DNA antibodies. Other autoantibodies, such as anti–double-stranded DNA, anti-Sm, and anti-Ro, are highly specific for the diagnosis of SLE and must in some way be linked to its pathogenesis (Table 1). Some marker autoantibodies serve as excellent diagnostic correlates of scleroderma [antitopoisomerase I, or Scl-70 (182)], of myositis [antihistidyl tRNA synthetase (183)], or of Sjögren's syndrome (anti-Ro and anti-La). Some of these autoantibodies are exquisitely specific for their autoantigens and are hard, if not impossible, to generate by deliberate immunization of rabbits or other experimental animals (87,184).

Individual patients with SLE tend to have distinctive profiles of autoantibodies that remain stable throughout the course of the illness. While the patient-to-patient variability in antibody spectrum is undoubtedly due in part to genetic diversity, it is surprising that even genetically homogeneous inbred mice show considerable differences in their autoantibody levels. Inbred mice maintained in the same colony under the same conditions have sharp differences in their autoantibody specificities. The anti-Sm response of MRL/*lpr* may give insight into the genesis of SLE autospecificities. Only about 25% of these mice develop anti-Sm, regardless of colony. Antibody levels show a true bimodal distribution; that is, anti-Sm-negative MRL/*lpr* mice have negligible amounts of anti-Sm, comparable to that of normal mice. When the lineage and microenvironment of anti-Sm–positive mice were traced, no genetic or environmental clustering could explain the appearance of autoantibody in certain mice but not others. The occurrence of the anti-Sm specificity in only a minority of mice was not due to the use of an uncommon V gene, nor to unusual gene rearrangements. These findings, which probably apply to antiribosomal P and anti-Su in MRL/*lpr* mice, have been interpreted as reflecting stochastic influences on the autoantibody repertoire of individuals. The individual variability in the laboratory, and perhaps the clinical manifestations of SLE and other autoimmune diseases, may arise from analogous poorly understood stochastic influences (185).

Systemic Lupus Erythematosus

SLE is a multisystem disorder that most frequently affects young women. Arthritis, skin rash, central nervous system dysfunction, and renal disease are the most common clinical manifestations (186). The severity of illness has a remarkable tendency to fluctuate over time, confounding studies of drug treatment. Long-term survival is the rule, although there remain considerable morbidity and mortality, chiefly from renal disease (10).

Immunologic interest in SLE dates back to the 1940s, when elevated gamma-globulin levels were noted, and attention was called to marrow tart cells. The realization that the spontaneous neutrophil phagocytosis of nuclear material observed *in vivo* could also be seen in buffy coat preparations from patients, and could be induced in normal buffy coat cells by addition of patient serum, gave rise to the notion that antibodies to nuclear material were of key importance. This led to many investigations of SLE antinuclear factors, demonstrated to be IgG, and to the development of a universal highly sensitive test for SLE, the fluorescent antinuclear antibody test (FANA) (187). More than 95% of SLE patients have positive FANAs, and furthermore, that the pattern of fluorescence staining was related to the antinuclear antibodies present in individual SLE serum (188). Diffuse staining, for example, was shown to be due to antibodies to histones and other DNA-binding proteins, rim staining to be due to antinative DNA, and a speckled pattern to reflect antibodies to components of the splicing apparatus, such as snRNPs. Some antibodies, detected by more specific methods, such as double immunodiffusion or ELISA, are quite specific for SLE (anti-Sm, anti-Su, anti-Ro, anti-La, and antinative DNA, for example).

Although SLE is best known for its array of antinuclear antibodies, antibodies to many other self components are well described. With the exception of IgG, the antigens tend to be cell-bound (e.g., antibodies to lymphocytes, platelets, erythrocytes, neutrophils, and basement membranes). In the case of IgG and clotting factors, it is possible that the true autoantibody target is cell-bound, in the form of immune complexes or of activated clotting factors.
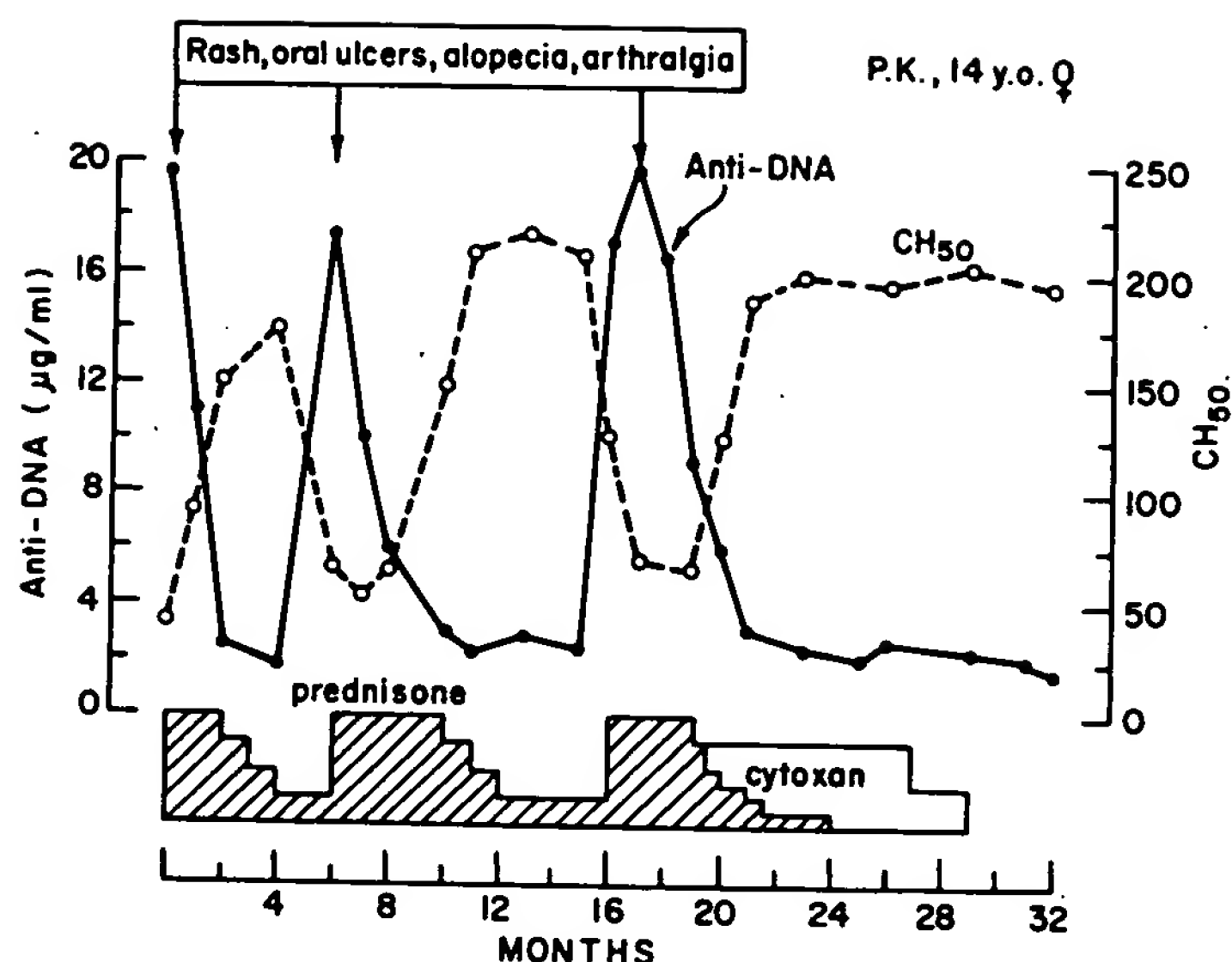
FIG. 3. Clinical course of a patient with systemic lupus erythematosus. Note the "mirror image" pattern of levels of anti-DNA antibodies and hemolytic complement (CH_{50}) in the serum. Exacerbations of the disease (*vertical arrows*) coincide with increased levels of anti-DNA antibodies.

Despite the wealth of information regarding SLE autoantibodies, it is useful to realize that only a few are implicated in disease pathogenesis. SLE renal disease has been attributed to DNA–anti-DNA complexes trapped in glomerular endothelium and epithelium, presumably triggering complement-mediated vascular injury and inflammation (189). This mechanism is supported by a correlation between anti-DNA levels and active renal disease when patients are followed serially, by an inverse correlation with circulating complement levels (Fig. 3) and by the finding of concentrated DNA–anti-DNA complexes in eluates from SLE glomeruli (190). Even for renal disease, however, studies supporting such immune-complex involvement for all histopathologic types are conflicting.

Although, presumably, nonrenal manifestations of SLE are autoantibody-mediated, few mechanistic data exist, except for the various cytopenias, for which an immune basis is well supported. Inflammatory skin disease (Fig. 4) appears to be T cell–mediated, although antibodies to Ro and La may be of importance (191). Infants born to SLE patients occasionally have thrombocytopenia and lesions typical of subacute cutaneous SLE, together with the Ro and La antibodies typical of this condition (192). Transplacental passage of IgG autoantibodies from mother to fetus explains the infant disease, as well as its spontaneous resolution, which is coincident with the disappearance of maternal antibody. Presumably, the heart block often seen in infants born to anti-Ro–positive mothers is also mediated by antibody that damages the developing cardiac conduction system.

Several other SLE manifestations have been difficult to relate to immune processes. Central nervous system involvement can lead to psychosis, seizures, and debilitating neurologic deficits (193). Nervous system tissue from affected patients is usually devoid of immunoglobulin deposition or evidence of cellular infiltration, the only usual finding being microvascular changes. Immunologic studies of arthritis and of pleural and pericardial inflammation are few, and an immune basis can be only presumed.

Rheumatoid Arthritis

RA is a common chronic inflammatory polyarthritis of worldwide distribution, with a female predominance of 3:1 and a peak onset in the fourth decade of life. Intense inflammation occurs in synovial joints, so that the normally delicate synovial membrane becomes infiltrated with mononuclear phagocytes, lymphocytes, and neutrophils (194). An inflammatory fluid is usually exuded by the inflamed synovium. In addition to pain and loss of mobility of joints, patients frequently develop systemic manifestations, namely anemia, subcutaneous nodules, pleurisy, pericarditis, interstitial lung disease, and manifestations of vasculitis such as nerve infarction, skin lesions, and inflammation of the ocular sclera. The course of RA is variable, but usually patients develop progressive loss of cartilage and bone around joints, with resulting diminished mobility.

Although the cause of RA remains unknown, a number of its features are suggestive of an autoimmune etiology. The pathology of arthritic joints suggests a T cell–mediated chronic inflammatory reaction (195,196). Susceptibility to RA is significantly greater in individuals with the DR4 haplotype, owing to the QKRAA motif in the hypervariable region, thereby suggesting a role for autoantigen presentation (197). Most patients (more than 80%) develop RF (19), mostly produced in the marrow, but with significant production by the inflamed synovium (198). The presence of intrasynovial immune complexes, together with diminished levels of complement components, implies an involvement of RF in some of the local pathology (199). In recent years, however, much interest has focused on the T cells and mononuclear phagocytes infiltrating the

FIG. 4. Photosensitive rash in a patient with SLE. Note the erythematous and scaly quality of the rash, which crosses the bridge of the nose and gives rise to a "butterfly" pattern. No skin rash was noted in areas of the skin usually covered by clothing.

joint. T cells are probably polyclonal (187), although evidence for selective expansion of certain Vβ subsets exists and has led some investigators to propose a role for superantigens (200). Depletion of T cells by thoracic duct drainage (201) or by immunosuppressive drugs, such as cyclosporine, has resulted in improvement, implying an important role for T cells in the inflammatory process (202). Much work on intrasynovial cytokines, however, has pointed toward mononuclear phagocytes as the prime driving force of the inflammatory process (203).

The synovial fluid in RA contains primarily cytokines of mononuclear origin, namely, IL-1, IL-6, and TNF-α. IL-1 receptor antagonist can also be demonstrated in most fluids. In contrast, IL-2, IFN-γ, and other T-cell cytokines are usually present in only small quantities, with the possible exception of IL-17. Efforts to treat RA with T cell–depleting monoclonal antibodies have yielded disappointing results (204). In contrast, administration of monoclonal antibodies to TNF-α has resulted in marked reduction of inflammation (205). Modest improvement has also been reported for antibodies to IL-6 and with administration of IL-1 receptor antagonist.

Efforts to define the underlying etiology of RA have met with frustration. Numerous reports of isolation of viruses, mycoplasmas, and other infectious agents have not been confirmed. Because experimental anti-collagen immunity in rodents results in an RA-like syndrome (206), it is possible that similar autoimmunity might be at work in RA. Although low levels of anti-collagen antibodies

and reactive T cells have been reported in RA, there is little to support the involvement of anti-collagen immunity in this disorder (207).

The mechanism whereby joint inflammation results in cartilage and bone erosion in RA is incompletely understood (208). It seems unlikely that leakage into cartilage of neutrophil or mononuclear phagocyte-derived proteolytic enzymes is responsible. The diffusion through the cartilage matrix of cytokines, such as IL-1 and IL-6, probably stimulates breakdown of cartilage and bone through an action on chondrocytes and osteoclasts. The destruction of cartilage and bone is functionally much more devastating than the joint inflammation.

Reactive Arthritis and the Spondyarthritides

An important group of rheumatic diseases is characterized by inflammation mostly of large joints, with a predilection for the sacroiliac joints in chronic cases, often associated with infection by certain organisms, or with psoriasis or inflammatory bowel disease (209). These illnesses share a tendency for inflammation to heal with brisk fibroblastic proliferation, together with the formation of new bone. They are unlike RA in that periarticular cartilage loss and osteopenia are uncharacteristic. A remarkable feature of these illnesses is their association with the HLA-B27 class I MHC allele. For Reiter's disease, a form of reactive arthritis that often includes genitourinary, oral mucosal, uveal tract, and skin inflammation, approximately 90% of afflicted individuals have the B27 haplotype, compared with 7% of the normal population (210). Numerous outbreaks of Reiter's disease have been observed in HLA-B27–positive individuals following epidemic infections with diarrhea-causing bacteria (see below), as shown in Fig. 5.

Whether autoimmunity is operative in the pathogenesis of these forms of chronic arthritis is unclear (211). Autoantibodies to IgG are absent, as are antinuclear antibodies, and other autoantibodies are not described. There is some evidence that infection with inciting organisms (which include *Chlamydia, Yersinia, Salmonella,* and *Shigella*) may elicit antibodies or cell-mediated immunity that is cross-reactive with self antigen, but the pathogenesis of these illnesses is quite unclear (212). The class I association has given rise to the speculation that CD8 T cells are important in mediating self-reactivity, and this contention is supported by the occurrence of Reiter's disease, often severe, in HIV-infected individuals with severely depressed CD4 counts yet relative preservation of CD8+ T cells (213).

Rats expressing a human HLA-B27 transgene in high copy number develop arthritis, inflammatory bowel disease, and skin lesions (214). These are less severe in animals raised under germ-free conditions, implying a role for microbial flora. T cells are required for development of disease. Imposition of the HLA-B27 transgene in mice lacking class I MHC molecules also gives rise to a Reiter's-like arthritic and inflammatory syndrome (215).

Systemic Vasculitis

The susceptibility of the vascular system to injury from deposition within vessel walls of immune complexes or from intravascular cell-mediated lesions is the basis of a large group of disorders with multiple manifestations that depend on the severity of involvement and the nature of the affected blood vessel (216). Figure 6 shows typical involvement of a medium-sized artery. In
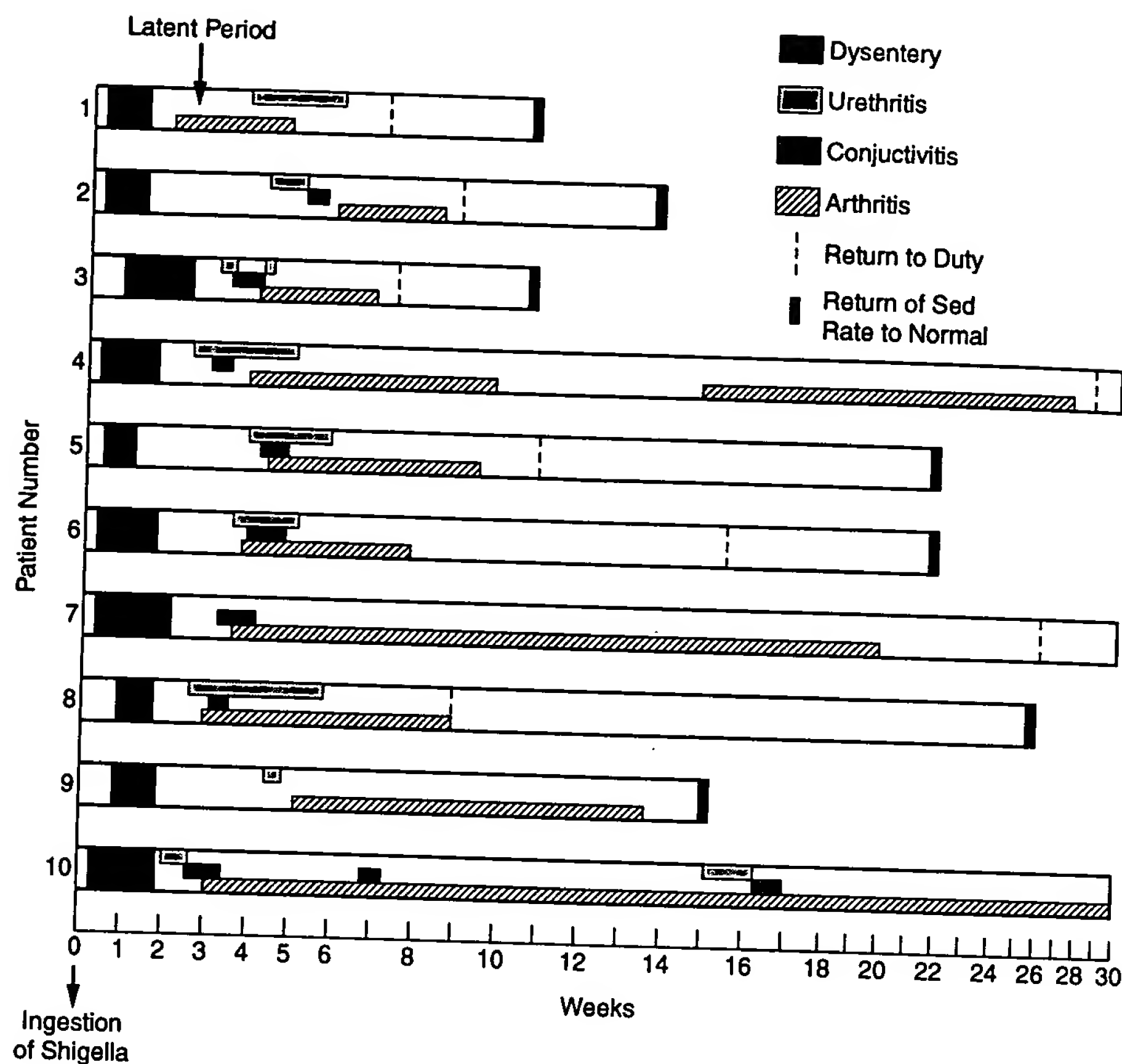
FIG. 5. The evolution of an outbreak of reactive arthritis among the crew of a naval vessel following an epidemic of *Shigella* dysentery is shown. Of over 600 crew members who developed diarrhea, only 11 developed features of Reiter's syndrome. Five of these sailors were traced 10 years later, and four were found to be HLA-B27–positive. (Reprinted from Noer HR. An "experimental" epidemic of Reiter's syndrome. *JAMA* 1966;198:693–698, with permission.)

some cases, the mechanism is immune complexes formed in response to exogenous antigens, such as viruses (especially hepatitis B and C) or drugs (217), while in other instances, autoantibodies or antibodies to as yet uncharacterized environmental agents are responsible.

Autoimmune vasculitis can be seen alone or together with SLE or other rheumatic diseases. Figure 7 demonstrates the deposition of C3 in the lumen of an inflamed small artery from an SLE patient with vasculitis. There is evidence for deposition of complexes of DNA–anti-DNA and IgG RF–IgG, with subsequent injury involving the complement system (218). On occasion, clinical disease correlates with cryoprecipitation of complexes in serum cooled below body temperature. A special example of vasculitis is that of mixed cryoglobulinemia (219), in which a monoclonal IgM (the product of a single aberrant B-cell clone) with autoantibody activity against IgG (i.e., RF activity) forms large circulating complexes that deposit in the walls of small and medium-sized arteries, causing ischemia and infarction of skin, nerves, and kidney.

Vasculitis manifestations can range from skin lesions alone (small vessel vasculitis) to ischemia of vital organs such as kidney, heart, brain, and liver. Attempts have been made to classify vasculitis based on known versus unknown etiology and
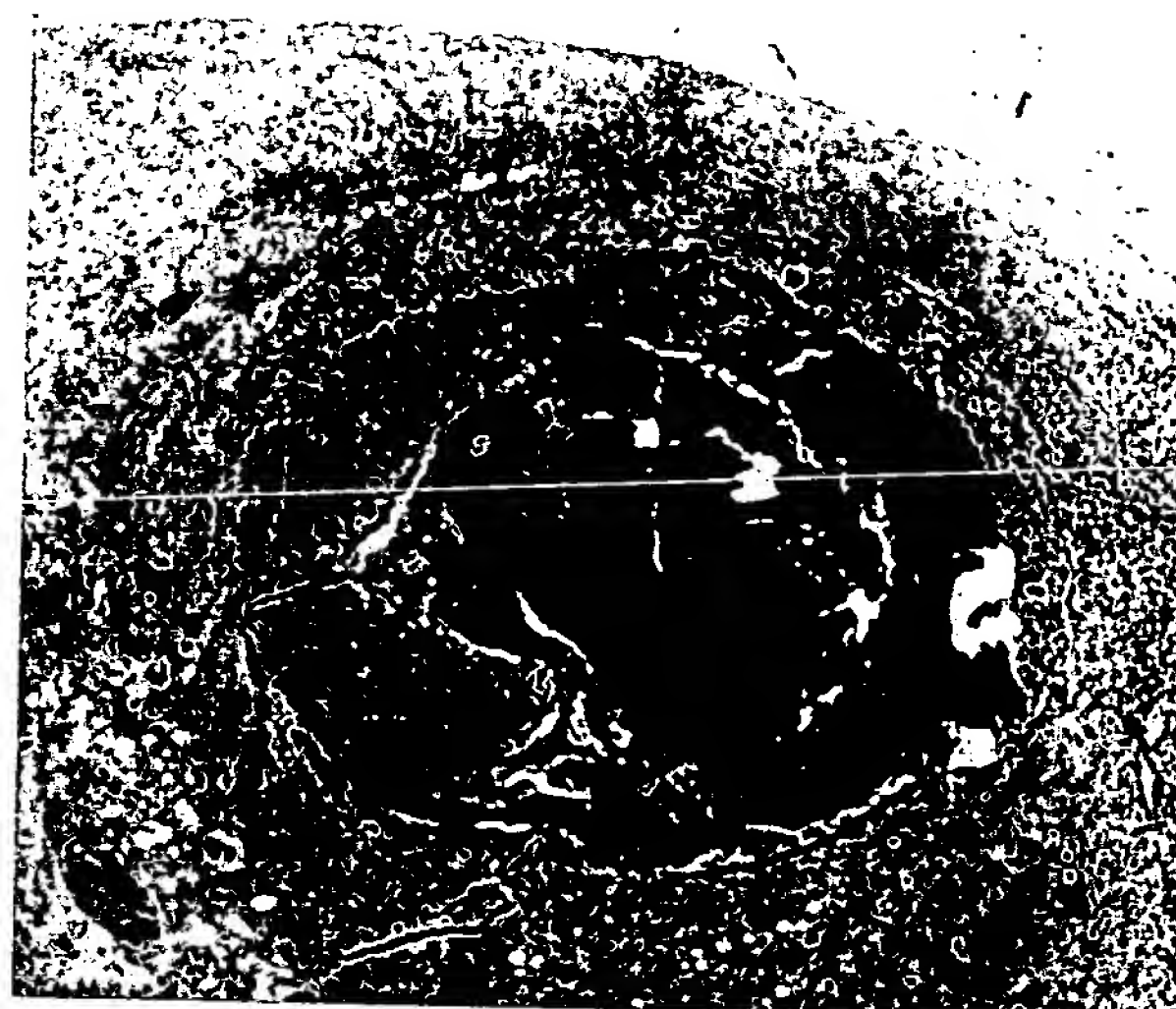

FIG. 6. Systemic necrotizing arteritis. Shown is a section of a subsegmental mesenteric artery of a 65-year-old man with severe abdominal pain and a bowel infarction. Note the disruption of the internal elastic lamina of the vessel, the intramural thrombus, and the leukocytic infiltrate. The patient had an excellent response to corticosteroids and cyclophosphamide.
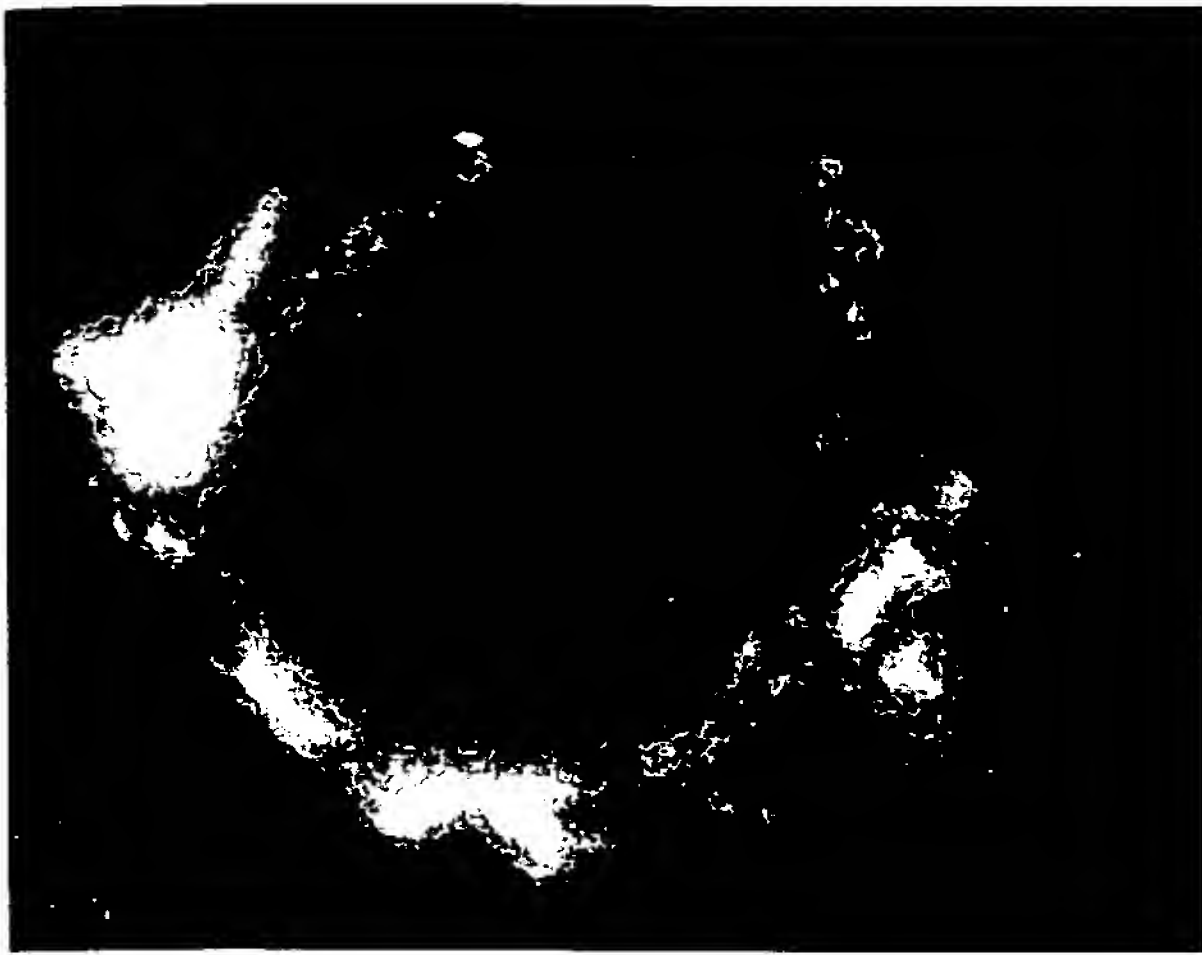
FIG. 7. Vasculitis in a patient with SLE. Note the presence of complement demonstrated using antihuman C3 in the wall of this artery.

rheumatic versus nonrheumatic. Figure 8 schematizes the type of involvement that results from inflammation of blood vessels of differing caliber.

Wegener's granulomatosis is a rare form of vasculitis featuring the formation of granulomas around blood vessels, with typical severe involvement of lung and kidney (220). The presence of antiproteinase 3 (c-ANCA) in most patients with this disorder has led to the hypothesis that ANCA-induced neutrophil activation is central to a chain of events leading to T-cell activation and a cellular immune response involving macrophage activation (221).

Sjögren's Syndrome

This lymphoproliferative and autoimmune disorder occurs in a primary form, not associated with a rheumatic disease, and as a complication of RA, SLE, or scleroderma. Patients develop infiltration of exocrine glands, mostly salivary and lacrimal glands, with activated polyclonal CD4+ T cells, together with hypergammaglobulinemia, autoantibodies, and, sometimes, vasculitis (222). Lymphocyte infiltration may extend beyond the exocrine glands to involve lungs, liver, and other viscera. Primary Sjögren's syndrome is associated with HLA-DR3 and with antibodies to Ro and La. There is an increased susceptibility to lymphoid malignancy, mostly B-cell lymphomas. An entity closely resembling Sjögren's syndrome has been described in HIV infection, with CD8- rather than CD4-bearing cells infiltrating exocrine glands (223).

Chronic Graft-Versus-Host Disease

In animals undergoing GVHD against class II determinants, a systemic autoimmune syndrome with SLE-like features produces antinuclear antibodies, immune-complex renal disease, and immune cytopenias (224). Clinical manifestations vary according to background genes and according to the genetic barrier between strains: I-E differences generate higher levels of antinuclear antibodies, yet I-A differences result in more renal disease. In murine chronic GVHD, induced across an MHC class II barrier, T and B cells interact in a cognate, MHC-restricted fashion, implying a specific form of T-cell help rather than the nonspecific effect on B cells of excessive cytokines (225).

"Homologous disease" occurs in rats subjected to chronic GVHD. Extensive sclerotic visceral lesions that are very like scleroderma occur (226). In human recipients of bone marrow, a chronic GVHD
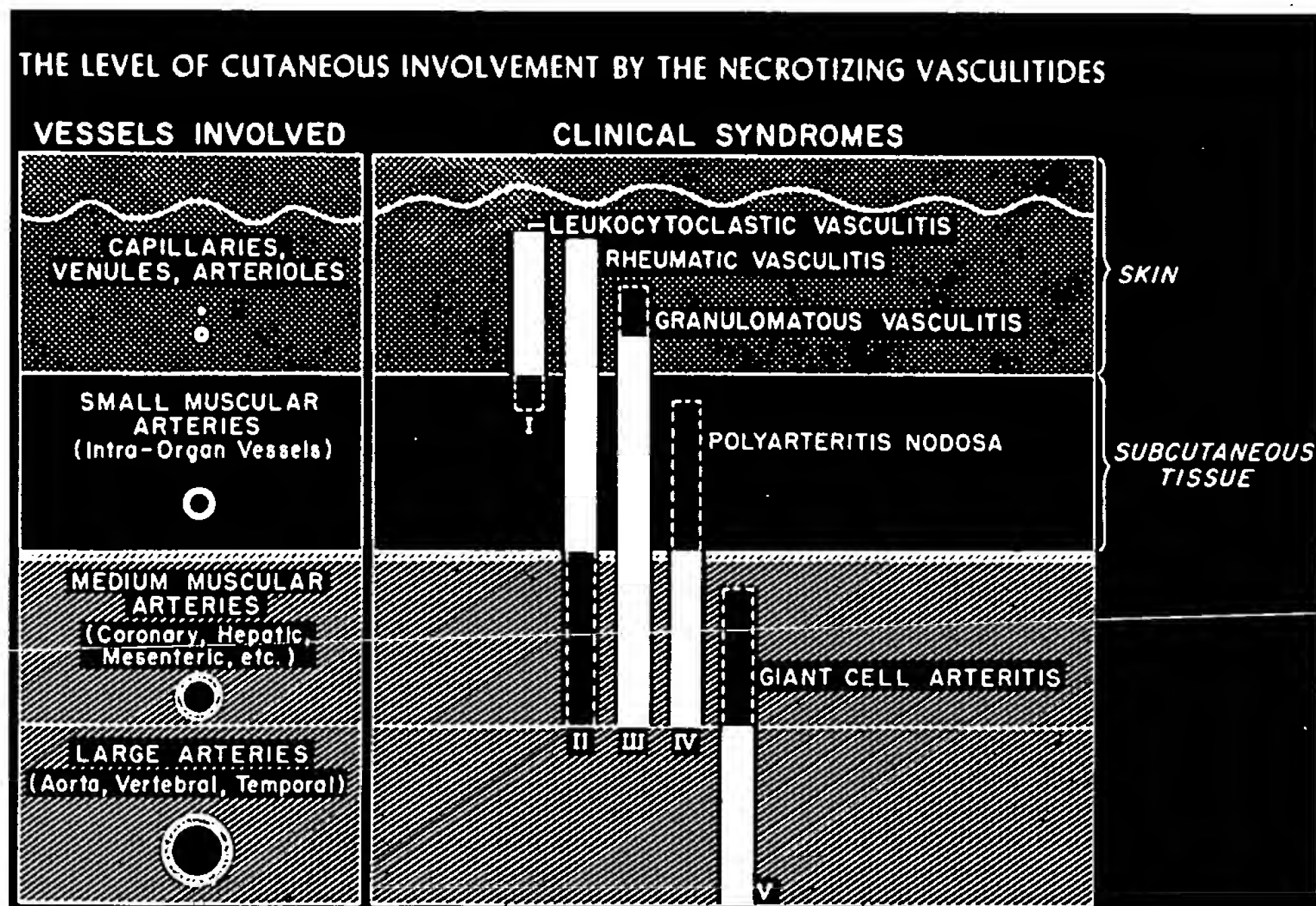

FIG. 8. The spectrum of vasculitis. The manifestations of vasculitis are dependent on the caliber of the involved vessel, which may in turn reflect the size, charge, or other physical properties of deposited immune complexes. Note that the resulting disease is dependent on the size of the inflamed vessel. (Courtesy of James A. Gilliam, M.D.)

syndrome is a major clinical problem, leading to fibrosis, skin pathology, and autoantibodies. The syndrome occurs even in recipients of autologous marrow, although in a milder form (227).

Scleroderma (Systemic Sclerosis)

This disease is marked by inflammation, followed by deposition in skin and viscera accompanied by certain antinuclear antibodies (228). Early lesions contain T-lymphocytes, and there is evidence of bias of the T-cell repertoire (229). Antibodies to topoisomerase I (Scl-70) correlate with visceral damage, and antibodies to centromere antigens connote a more benign course (230). Scleroderma is characterized by marked vascular abnormalities, the most dramatic of which is the episodic reduction in peripheral arterial perfusion (often provoked by cold temperatures), known as Raynaud's phenomenon. Impairment of circulation can lead to pain, infections, and ischemic amputation of the distal fingertips. Considerable disability can result from this and from the loss of hand mobility due to thickening of the overlying skin.

Patients with the severe form of scleroderma, known as progressive systemic sclerosis, develop serious injury to the skin, kidney, lung, and gastrointestinal tract. Therapy is usually ineffective. Despite the clear-cut evidence of serologic autoimmunity, the autoimmunity underlying the visceral and skin damage in the illness is only presumed, and nothing is known of the basic mechanism. A strain of chickens develops an illness with marked scleroderma-like features (231).

COMMONLY USED ANIMAL MODELS OF SYSTEMIC AUTOIMMUNE DISEASE

Several spontaneous murine models have been widely used to address SLE pathogenesis and treatment.

Lpr and gld Mice

The autosomal recessive *lpr* mutation of the Fas apoptosis gene causes progressive, spectacular lymphadenopathy (Fig. 9), multiple SLE-like autoantibodies, and hypergammaglobulinemia (232). As is also true for the other murine SLE models (*vide infra*),
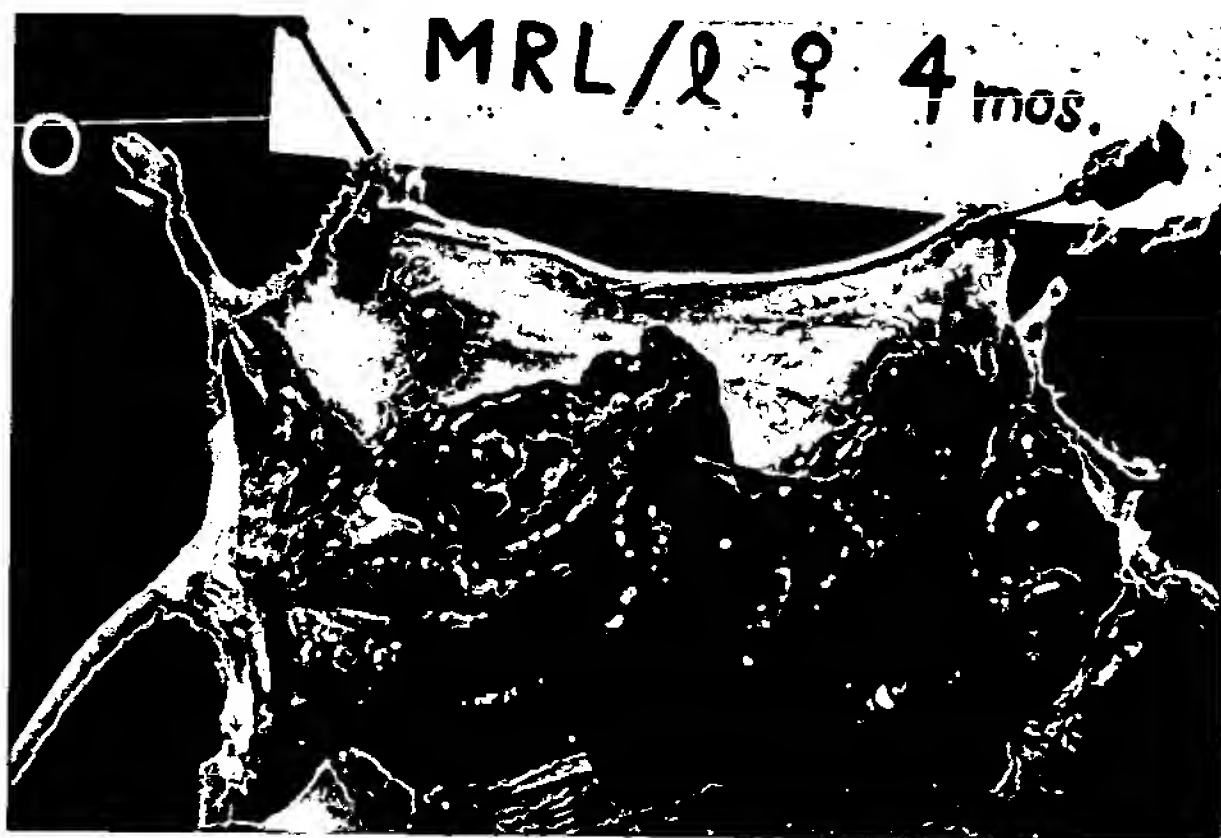

FIG. 9. MRL/*lpr* mouse (age 4 months). Note massive lymph node and spleen enlargement due to CD4⁻CD8⁻ T-cell infiltration. (Courtesy of Robert Eisenberg, M.D.)

expression of laboratory and clinical manifestations of disease is highly dependent on other, poorly understood background genes (233). Thus, MRL/*lpr* mice, which are the best-studied strain, develop severe glomerulonephritis and vasculitis and have a markedly foreshortened life span, while C57BL6/*lpr* (B6/*lpr*) mice manifest a milder syndrome, with nearly normal longevity. The *gld* gene leads to essentially identical syndromes on similar backgrounds.

The failure of the Fas/FasL system to delete autoreactive extrathymic T cells accounts for the accumulation of vast numbers of CD4⁻CD8⁻ anergic T cells, the unusual phenotype of which apparently represents a secondary mechanism for downregulating function, in the absence of deletion. The Fas mutation is also expressed in B cells, leading to a failure to delete autoantibody-forming cells but not to lymphoproliferation analogous to T cells (234).

T cells are required for development of both lymphadenopathy and autoantibodies. In *lpr* mice with deletion of MHC class II genes (235), or those lacking CD4 molecules (236), autoantibodies fail to develop, yet lymphadenopathy occurs; conversely, the absence of CD8 or β2-microglobulin (237) results in little change in autoantibody levels, but a marked decrease in lymphadenopathy. These and other studies support the idea that the abnormal double-negative T cells of *lpr* are descended primarily from CD8 precursors, which lose their CD8 as part of their evolution into anergic cells. The T cells that provide help for autoantibodies, on the other hand, are primarily CD4-bearing cells that recognize antigens (and presumably autoantigens) in the context of self class II MHC.

NZB and NZB/NZW F1 Mice

NZB mice develop autoimmune hemolytic anemia, antinuclear antibodies, and late-life lymphoreticular neoplasms (238). The F1 offspring of this strain and near-normal NZW mice suffer from a much more fulminant and SLE-like syndrome, leading to diffuse proliferative glomerulonephritis, high-titer antinuclear antibodies, and early death (especially in females). NZB×SWR F1 mice are another well-studied model that develops renal disease, offering the additional advantage that the SWR parents are free of endogenous retroviruses and without apparent additional immunopathology (239). The genetics of SLE in NZB crosses are complex and are discussed elsewhere. The SLE-like disease is characterized by both B- and T-cell defects, notably B-cell hyperactivity, even in fetal life, and a requirement for T cells for development of autoantibodies and disease (240).

BXSB Mice

These animals develop an age-dependent SLE-like syndrome that is much more severe in males because of a Y-chromosome gene (Yaa) (241). Unlike the *lpr* mutation, which provokes at least some degree of autoimmune disease regardless of genetic background, Yaa results in acceleration of autoimmunity only when bred onto the genomes of autoimmune mice. High-titer antinuclear antibodies and immune-complex nephritis lead to early mortality in males. Chimera studies using B6-Yaa mice have shown that it is largely the T-lymphocytes that are responsible for the autoimmune disease, as their elimination, but not the elimination of B cells, reduces disease in chimeras. It has been suggested that the basic defect in this strain involves enhanced T-B interaction, possibly through abnormal adherence. The presence of a functional I-E molecule reduces serologic

and clinical disease, possibly through presentation of peptide fragments of I-E by the I-A element (242).

Induction of Systemic Lupus-like Syndrome in Mice through Injection of Pristane

Pristane, a branched alkane, is widely used to produce peritoneal inflammation, which primes mice for subsequent hybridoma implantation. It was fortuitously observed that mice receiving pristane alone developed a progressive autoimmune syndrome marked by development of SLE-like autoantibodies, including anti-Sm and other highly characteristic specificities (243). SLE-like glomerular changes are observed, together with deposition of immunoglobulin and complement. Serologic features of the syndrome are dependent on the genetic background of the mouse, with H-2 playing a prominent role. For instance, H-2^s mice develop antiribosomal protein autoantibodies, while autoantibodies appear only in low titer in H-2^b-expressing C57BL mice (244).

Systemic Autoimmunity Induced by Idiotype Infusion

A syndrome characterized by antinuclear antibodies, cytopenias, and immune-mediated renal disease occurs in mice given antibodies expressing the human 16/6 idiotype, which is found on certain human IgM monoclonal anti-DNA antibodies (245). Disease is preceded by antibodies to the 16/6 idiotype, and may represent precipitation of a cascade of aberrant idiotype–antiidiotype network interactions involving T cells, as SLE manifestations can also be induced by T-cell lines from idiotype-immunized mice (246). These mice have also been reported to have anticardiolipin antibodies and abnormalities of hemostasis.

The Viable Motheaten Mouse

Research has shown that the lethal motheaten (me) and viable motheaten (me^v) phenotypes, which result in a severe neonatal autoimmune syndrome with hypergammaglobulinemia and autoantibodies to DNA and erythrocytes, are due to a mutant tyrosine kinase expressed in hematopoietic cells (247). Virtually all of the mouse B cells are of the B1 subset, and death from an apparent autoimmune and inflammatory disease occurs by 3 weeks. The mechanism whereby the kinase deficiency results in autoreactivity is unclear, but it presumably reflects fundamental mechanisms controlling B-cell differentiation.

Severe Autoimmune Disease in Knock-out and Transgenic Strains

Mice homozygous for deletion of the transforming growth factor-β (TGF-β) gene suffer a severe and fulminant autoimmune disorder that is characterized by multiorgan inflammatory disease and death by 3 weeks. The disorder is mediated by T-lymphocytes and can be adoptively transferred to MHC-compatible normal mice (248). Apparently, the absence of the immunosuppressive and antiinflammatory effects of TGF-β permits unregulated spontaneous inflammatory disease. A parallel situation occurs in mice without functional CTLA4. The absence of negative regulation of T cells, which is normally mediated by this molecule, also leads to a severe neonatal autoimmune and inflammatory disease (249).

Striking autoimmune disease, especially involving the intestinal tract, but with hematologic and other systemic manifestations as well, occurs in mice with deleted IL-2 (250), IL-4 (251), and TCR genes (252). To some extent, the inflammatory disease is dependent on the microbiologic environment of the mice as well as the background strain, and has been attributed to the consequences of cytokine imbalances.

Mice transgenic for the bcl-2 oncogene expressed in B cells develop certain SLE-like autoantibodies (253). The combination of the bcl-2 apoptosis defect and the *lpr* Fas mutation results in mice with even further lymphoid hyperplasia, but no further increase in autoantibodies, suggesting that the apoptosis impairment resulting from the *lpr* mutation is maximal in terms of autoantibody production and cannot be further exacerbated (254).

The Tight-skin Mouse

The *tsk* mutation is a dominant mutation on chromosome 2, which is lethal in its homozygous form (255). The mice develop progressive skin tightening, together with pulmonary fibrosis and cardiomyopathy. Antibodies to topoisomerase I (256) and RNA polymerase I have been detected. Mice lacking CD4 cells fail to develop skin lesions, but develop visceral abnormalities; lack of CD8 cells has little influence on disease (257).

Models of Rheumatoid Arthritis

Several rodent models of RA have been widely used (258). A chronic polyarthritis results from the injection of peptidoglycan–polysaccharide in rats, with extensive joint destruction (259). It is dependent on the genetic background of the rat (Lewis is the prototype susceptible strain; Buffalo is resistant), partly due to MHC genes, and requires T-lymphocytes. Considerable evidence suggests that the inflammatory disease is due to the persistence of bacterial debris. A relapsing form of the disease can be induced by intraarticular bacterial LPS in animals that have had an earlier injection of peptidoglycan–polysaccharide (260).

A chronic inflammatory arthritis, also in general use, is induced by immunization with type II collagen in adjuvant (261). Collagen arthritis is mainly due to T-cell immunity to type II collagen, although antibody is also demonstrable and may provoke some of the injury. MHC influences and T-cell oligoclonality are important in this illness (262). A single injection of complete Freund's adjuvant alone causes a chronic arthritis in rats but not in mice. It has been used as a way of evaluating antiinflammatory drugs.

One of the most interesting more recent models of RA is the inflammatory arthritis in mice transgenic for human T-cell leukemia virus type I (HTLV-I) *tax* (263). Such animals develop chronic erosive arthritis with synovial proliferation and pathologic changes resembling RA. They produce anticollagen antibodies, RF, and anti–heat-shock proteins, and they also manifest T-cell immunity to collagen and heat-shock proteins. A Sjögren's-like autoimmune exocrinopathy has also been reported in these animals (264). These findings are of special interest because humans with HTLV infection may also develop inflammatory arthritis, alone or in the presence of myelopathy (265).

Mice transgenic for TNF-α also develop a spontaneous erosive arthritis, presumably due to the proinflammatory action of this cytokine (266). These studies support the proposed key role of TNF-α in RA.

IMMUNE INJURY IN SYSTEMIC AUTOIMMUNE DISEASE

The classification scheme of Gell and Coombs is still a useful way of subdividing injury mechanisms in systemic autoimmunity. Type I injury, mediated by IgE, is not important in these disorders. By contrast, tissue damage initiated by binding of autoantibody directly to target tissues is of importance, particularly in organ-specific autoimmune disease, but, to a great extent, also in systemic autoimmune disease, in which antibodies to cell and basement membranes, fibronectin, collagen, and other fixed components of tissue may exist. Binding of antibody to self tissue leads to inflammation through a complex series of events involving the complement and coagulation pathways, leading to chemotaxis of neutrophils and monocytes and to their phagocytosis and release of local inflammatory mediators. Platelet aggregation, dilatation of vascular smooth muscle, and activation of mast cells are all part of the series of events triggered by autoantibody binding to tissue in type II injury; these topics are discussed in detail elsewhere in this textbook. Examples of autoantibodies provoking these changes probably include anticollagen antibodies and antiglomerular basement antibodies. Figure 10 depicts the pathologic changes in Goodpasture's syndrome, a disorder that causes hemorrhagic lung and kidney lesions due to antibodies directed against the basement membrane proteins common to both organs.

Type III injury, mediated by immune complexes, is believed to account for much of the pathology of systemic autoimmune diseases, particularly SLE and vasculitis. In NZB/NZW mice, blocking of C5 using monoclonal antibody reduces nephritis and increases survival, supporting a role for classical pathway activation in the immune-complex disease of this strain (267). The protean nature of immune complexes, which can range from just a few molecules of antigen and antibody to huge complexes involving whole cells coated or cross-linked by antibody, accounts for the great variety of pathology encountered in type III injury. Much interest has focused on defining the offending antigens that are present in injurious immune complexes in SLE and related diseases, but with mixed success. SLE exacerbations are frequently preceded or accompanied by a fall in hemolytic complement, together with a rise in levels of antibodies to native (double-stranded) DNA. These antibodies are concentrated in the glomeruli of patients with SLE renal disease (Fig. 11), consistent with the idea that DNA-anti-DNA complexes may deposit in SLE kidneys and provoke inflammation (268). Although it seems likely that DNA-anti-DNA is an important antibody system in SLE renal disease, it is very likely that other kinds of autoantibodies also contribute in important ways to glomerular injury (189). Antichromatin, for example, forms immune complexes that may localize on the glomerular basement membrane. Current studies focus on the charge, size, and antigenic characteristics of such antibodies in relation to their ability to bind and to injure glomeruli.

Type IV injury is due to T-lymphocytes, macrophages, and perhaps other cells that infiltrate tissues, sometimes causing granulomas. Some systemic autoimmune diseases are dominated by type IV injury, for example, Wegener's granulomatosis; yet it is more common for type IV mechanisms to coexist with types II and III. SLE, for example, is frequently accompanied by destructive and inflammatory skin lesions dominated by T-lymphocytes; similarly, the destructive inflammatory muscle lesions of polymyositis occur together with antisynthetase antibodies and other serologic autoimmunity. There may be some contribution of cell-mediated immunity to SLE renal disease, but expression of MHC class I or class II molecules is unnecessary for development of nephritis in MRL/lpr mice (269).

Autoantibodies may also exert damage through their effects on the coagulation system. The antiphospholipid syndrome is marked by arterial and venous thromboses, which may cause stroke, myocardial infarction, and thromboembolism. It is seen alone or as a feature of SLE and is due not to true antiphospholipid antibodies, but rather to antibodies to phospholipid-binding proteins, mainly β2-glycoprotein I (270). By an imperfectly understood mechanism, these antibodies enhance platelet aggregation and activation and promote thrombus formation while paradoxically prolonging the *in vitro* partial thromboplastin time, an indicator of coagulation. This *in vitro* phenomenon is termed the *lupus anticoagulant* and is present in a substantial minority of SLE patients as well as in many individuals with no other recognized illness. It is a major cause of

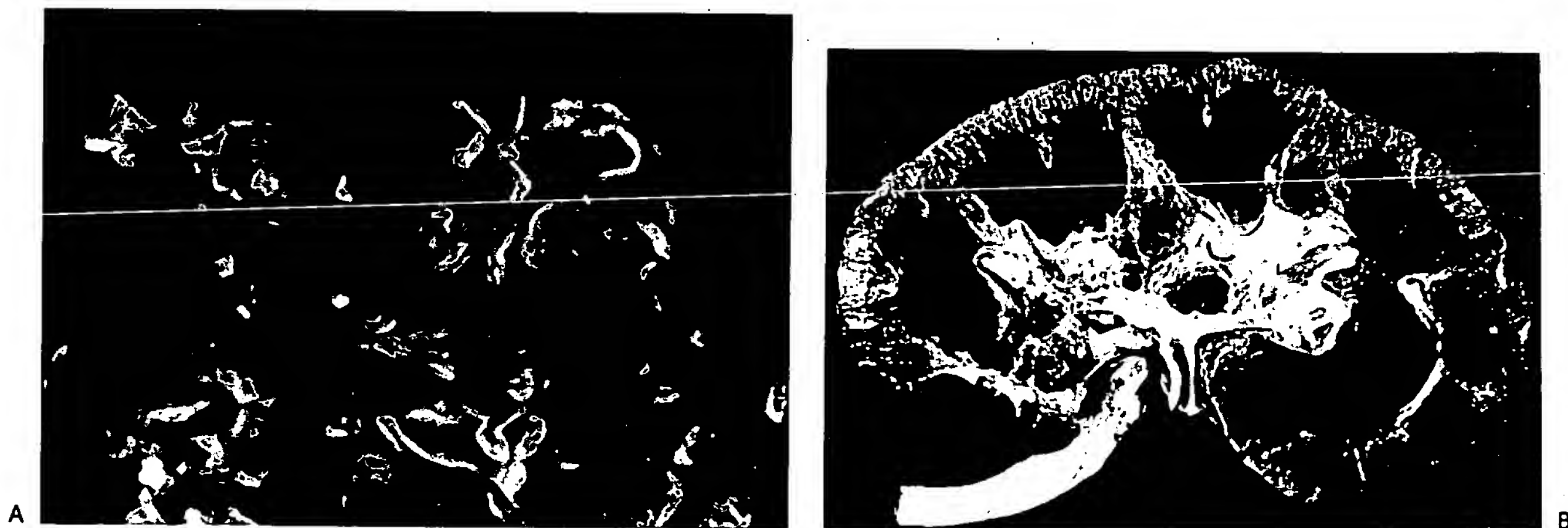**FIG. 10.** Type II immune-mediated injury. **Panel A:** Linear deposition of IgG against antigens present on the glomerular basement membrane of a patient with Goodpasture's syndrome is illustrated using fluoresceinated antihuman IgG. Similar changes were seen in the lung. **Panel B:** Hemorrhagic changes are visible in the gross autopsy pathology specimen from this patient. (Courtesy of William J. Yount, M.D.)
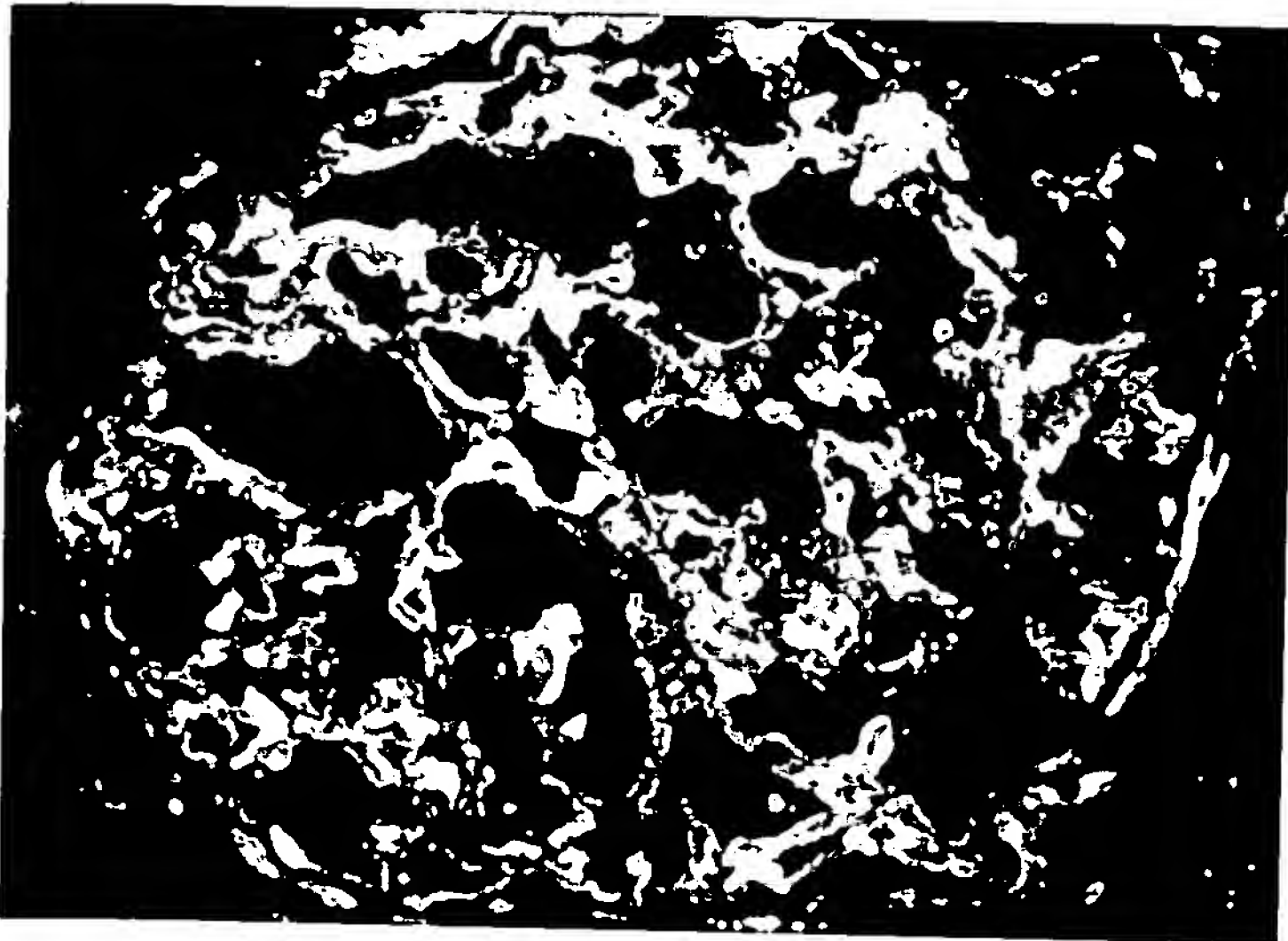
FIG. 11. Type III (immune-complex) injury in an SLE renal biopsy specimen. This patient had proteinuria and red blood cells in her urine. Note the granular (sometimes called "lumpy-bumpy") distribution of the immune deposits in this section stained with antibody to human C3.

early spontaneous abortion and may be an important cause of thrombotic disease in the general population.

Tissue damage may also be mediated through antibodies to neutrophil cytoplasmic antigens (ANCAs). These IgG antibodies, initially detected by immunofluorescence, have been divided by staining patterns into perinuclear (p-ANCA) and cytoplasmic (c-ANCA). p-ANCAs are directed against myeloperoxidase, while c-ANCAs are specific for proteinase 3 (221). These autoantibodies are useful markers for vasculitis, including Wegener's granulomatosis, pauciimmune necrotizing and crescentic pauciimmune glomerulonephritis, and polyarteritis nodosa, and their titers correlate with disease severity. The mechanism by which antibodies to these cytoplasmic antigens leads to blood vessel damage and inflammation is incompletely understood, but it may involve expression on activated neutrophils of proteinase 3 and myeloperoxidase, and possibly release of free proteinase 3. Antibodies to these molecules may provoke enhanced neutrophil chemotaxis and adhesion, together with triggering of the respiratory burst. This may lead to a series of events culminating in activation of T cells and macrophages and the formation of necrotizing granulomas.

APPROACHES TO THE TREATMENT OF SYSTEMIC AUTOIMMUNE DISEASE

In general, the management of human systemic autoimmune disease is empirical and unsatisfactory. For the most part, broadly immunosuppressive drugs, such as corticosteroids, are used in a wide variety of severe autoimmune and inflammatory disorders; in milder conditions, antiinflammatory agents acting on eicosenoid metabolism are often sufficient.

In addition to corticosteriods, other immunosuppressive agents are used in management of the systemic autoimmune diseases. Cyclophosphamide is an alkylating agent that causes profound depletion of both T- and B-lymphocytes and impairment of cell-mediated immunity. It is used in SLE nephritis and is particularly effective in granulomatous vasculitis and polyarteritis nodosa. Its use entails the risks of immunosuppression, along with an increased incidence of lymphoreticular malignancies. Azathioprine

and the closely related 6-mercaptopurine are used in parallel situations; these are somewhat less effective but are less toxic.

Cyclosporine, tacrolimus, and mycophenolate mofetil are natural products with specific properties of T-lymphocyte suppression, and they have been used with success in SLE, RA, and, to a limited extent, in vasculitis and myositis. They have significant renal toxicity in addition to their immunosuppressive effects.

Methotrexate is widely used as a "second-line" agent in RA, with the goal of reducing disease progression. It is also useful in polymyositis and other connective-tissue diseases. Its mechanism of action here is controversial and may relate to its action on adenosine receptors rather than to its more familiar role as an antimetabolite.

There is optimism that more specific treatment for autoimmune disorders can be devised when their mechanisms become better understood. Oral tolerance holds promise as a means of attracting immunosuppressive T-lymphocytes to sites of active autoimmune pathology and suppressing inflammation by a bystander effect, probably involving TGF-β (271). Other approaches under development are monoclonal antibodies that are intended to block the action of cytokines or to deplete lymphocytes (204). With the exception of anti–TNF-α in RA (205), these have been disappointing.

CONCLUSIONS

The mechanisms of systemic autoimmune disease are diverse and incompletely understood. Several points are worthy of emphasis. The rules and restrictions governing ordinary immune responses seem to apply to autoimmune responses: there is little that is extraordinary about the immunoglobulin or TCR genes used or in their means of rearrangement or diversification; antigen is required to initiate responses. Production of and response to cytokines and other mediators is similar to what is seen for responses to exogenous antigens, and T and B cells collaborate in an MHC-restricted fashion. The availability of transgenic and knock-out mice and continuing progress in the understanding of the genome seem likely to open novel and fruitful approaches to understanding disorders of systemic autoimmunity.

REFERENCES

1. Lahita RG. The connective tissue diseases and the overall influence of gender. *Int J Fertil Menopausal Stud* 1996;41:156–165.
2. Cervera R, Khamashta MA, Font J, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients: *Medicine* 1993;72:113–124.
3. Lahita RG. Low plasma androgens in women with systemic lupus erythematosus. *Arthritis Rheum* 1987;30:241–248.
4. Ahmed SA, Penhale WJ, Talal N. Sex hormones, immune responses, and autoimmune diseases. Mechanisms of sex hormone action. *Am J Pathol* 1985;121:531–551.
5. Lorber M, Gershwin ME, Shoenfeld Y. The coexistence of SLE with other autoimune diseaes: the kaleidoscope of autoimmunity. *Semin Arthritis Rheum* 1994;24:105–113.
6. Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease—an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). *Am J Med* 1972;52:148–159.
7. Gottlieb AB, Lahita RG, Chiorazzi N, Kunkel HG. Immune function in systemic lupus erythematosus: impairment of in vitro T-cell proliferation and in vivo antibody response to exogenous antigen. *J Clin Invest* 1979;63:885–892.
8. Hahn BH, Bagby MK, Osterland CK. Abnormalities of delayed hypersensitivity in systemic lupus erythematosus. *Am J Med* 1973;55:25–31.
9. Winfield JB, Winchester RJ, Kunkel HG. Association of cold-reactive anti-lymphocyte antibodies with lymphopenia in systemic lupus erythematosus. *Arthritis Rheum* 1975;18:587–594.
10. Estes D, Christian CL. The natural history of systemic lupus erythematosus by prospective analysis. *Medicine* 1971;50:85–95.
11. Ehrlich P, Morgenroth J. On haemolysis: third communication. In: *The collected papers of Paul Ehrlich*. F. Himmelweit, ed. vol 2. London: Pergamon, 1957:205–212.
12. Harrington WJ, Minnich V, Hollingsworth JW, Moore CV. Demonstration of a thrombocytopenic factor in the blood of patients with thrombocytopenic purpura. 1951. *J Lab Clin Med* 1990;115:636–645.
13. Rose NR, Witebsky E. Studies on organ specificity: V. Changes in the thyroid glands of rabbits following acute immunization with rabbit thyroid extracts. *J Immunol* 1956;76:417–423.
14. Burnet FM. A modification of Jerne's theory of antibody production using the concept of clonal selection. *Aust J Sci* 1957;20:67–69.
15. Kakkanaiah VN, Seth A, Nagarkatti M, Nagarkatti P. Autoreactive T cell clones isolated from normal and autoimmune-susceptible mice exhibit lymphokine secretory and functional properties of both Th1 and Th2 cells. *Clin Immunol Immunopathol* 1990;57:148–162.
16. Grabar P. Autoantibodies and the physiological role of immunoglobulins. *Immunol Today* 1983;4:337–339.
17. Hooper B, Whittingham S, Mathews JD, Mackay IR, Curnow DH. Autoimmunity in a rural community. *Clin Exp Immunol* 1972;12:79–87.
18. Hawkins BR, O'Connor KJ, Dawkins RL, Dawkins B, Rodger B. Autoantibodies in an Australian population. I. Prevalence and persistence. *J Clin Lab Immunol* 1979;2:211–215.
19. Chen PP, Fong S, Carson DA. Rheumatoid factor. *Rheum Dis Clin North Am* 1987;13:545–568.
20. Nemazee DA, Sato VL. Induction of rheumatoid antibodies in the mouse: regulated production of autoantibody in the secondary humoral response. *J Exp Med* 1983;158:529–545.
21. Welch MJ, Fong S, Vaughan J, Carson D. Increased frequency of rheumatoid factor precursor B lymphocytes after immunization of normal adults with tetanus toxoid. *Clin Exp Immunol* 1983;51:299–304.
22. Bonfa E, Llovet R, Scheinberg M, de Souza JM, Elkon KB. Comparison between autoantibodies in malaria and leprosy with lupus. *Clin Exp Immunol* 1987;70:529–537.
23. Roosnek E, Lanzavecchia A. Efficient and selective presentation of antigen-antibody complexes by rheumatoid factor B cells. *J Exp Med* 1991;173:487–489.
24. Tighe H, Heaphy P, Baird S, Weigle WO, Carson DA. Human immunoglobulin (IgG) induced deletion of IgM rheumatoid factor B cells in transgenic mice. *J Exp Med* 1995;181:599–606.
25. Tighe H, Chen PP, Tucker T, et al. Function of B cells expressing a human immunoglobulin M rheumatoid factor autoantibody in transgenic mice. *J Exp Med* 1993;177:109–118.
26. Chau V, Tobias JW, Bachmair A, et al. A multiubiquitin chain is confined to specific lysine in a targeted short-lived protein. *Science* 1989;243:1576–1583.
27. Klinman DM, Banks S, Hartman A, Steinberg AD. Natural murine autoantibodies and conventional antibodies exhibit similar degrees of antigenic cross-reactivity. *J Clin Invest* 1988;82:652–657.
28. Hartman AB, Mallett CP, Srinivasappa J, Prabhakar BS, Notkins AL, Smith-Gill SJ. Organ reactive autoantibodies from non-immunized adult BALB/c mice are polyreactive and express non-biased VH gene usage. *Mol Immunol* 1989;26:359–370.
29. Oldstone MBA. Molecular mimicry and autoimmune disease. *Cell* 1987;50:819–820.
30. Kieff E, Dambaugh T, Heller M, et al. The biology and chemistry of Epstein-Barr virus. *J Infect Dis* 1982;146:506–517.
31. Chen PP. From human autoantibodies to the fetal antibody repertoire to B cell malignancy: it's a small world after all. *Int Rev Immunol* 1990;5:239–251.
32. Casali P, Notkins AL. Probing the human B-cell repertoire with EBV: polyreactive antibodies and CD5+ B lymphocytes. *Annu Rev Immunol* 1989;7:513–535.
33. Murakami M, Tsubata T, Okamoto M, et al. Antigen-induced apoptotic death of Ly-1 B cells responsible for autoimmune disease in transgenic mice. *Nature* 1992;357:14–15.
34. Reap EA, Sobel ES, Cohen PL, Eisenberg RA. Conventional B cells, not B-1 cells, are responsible for producing autoantibodies in *lpr* mice. *J Exp Med* 1993;177:69–78.
35. Reap EA, Sobel ES, Jennette JC, Cohen PL, Eisenberg RA. Conventional B cells, not B1 cells, are the source of autoantibodies in chronic graft versus host disease. *J Immunol* 1993;151:7316–7323.
36. Casali P, Burastero SE, Balow JE, Notkins AL. High-affinity antibodies to ssDNA are produced by CD-B cells in systemic lupus erythematosus patients. *J Immunol* 1989;143:3476–3483.
37. Rajewsky K, Takemori T. Genetics, expression, and function of idiotypes. *Annu Rev Immunol* 1983;1:569–607.
38. Bona CA, Heber-Katz E, Paul WE. Idiotype-anti-idiotype regulation. I. Immunization with a levan-binding myeloma protein leads to the appearance of auto-anti-(anti-idiotype) antibodies and to the activation of silent clones. *J Exp Med* 1981;153:951–967.
39. Uner AH, Knupp CJ, Tatum AH, Gavalchin J. Treatment with antibody reactive with the nephritogenic idiotype, IdLNF1, suppresses its production and leads to prolonged survival of (NZB × SWR) F1 mice. *J Autoimmun* 1994;7:27–44.
40. Oukka M, Colucci-Guyon E, Tran PL, et al. CD4 T cell tolerance to nuclear proteins induced by medullary thymic epithelium. *Immunity* 1996;4:545–553.
41. Goldings EA. Defective B cell tolerance induction in New Zealand black mice I. Macrophage independence and comparison with other autoimmune strains. *J Immunol* 1983;131:2630–2634.
42. Rathmell JC, Goodnow CC. Effects of the *lpr* mutation on elimination and inactivation of self-reactive B cells. *J Immunol* 1994;153:2831–2842.
43. Staudt LM, Singh H, Sen R, Wirth T, Sharp PA, Baltimore D. A lymphoid-specific protein binding to the octamer motif of immunoglobulin genes. *Nature* 1986;323:640–643.
44. Nagarkatti PS, Snow EC, Kaplan AM. Characterization and function of autoreactive T-lymphocyte clones isolated from normal, unprimed mice. *Cell Immunol* 1985;94:32–48.
45. Sakane T, Steinberg AD, Arnett FC, Reinertsen JL, Green I. Studies of immune functions of patients with systemic lupus erythematosus. *Arthritis Rheum* 1979;22:770–776.
46. Saito K, Tamura A, Narimatsu H, Tadakuma T, Nagashima M. Cloned auto-la-reactive T cells elicit lichen planus-like lesion in the skin of syngeneic mice. *J Immunol* 1985;137:2485–2495.
47. Weston KM, Yeh ET, Sy MS. Autoreactivity accelerates the development of autoimmunity and lymphoproliferation in MRL/Mp-*lpr/lpr* mice. *J Immunol* 1987;139:734–742.
48. Deeg HJ. Graft-versus-host disease: host and donor views. *Semin Hematol* 1993;30:110–117.
49. Erkeller-Yusel F, Hulstaart F, Hannet I, Isenberg D, Lydyard P. Lymphocyte subsets in a large cohort of patients with systemic lupus erythematosus. *Lupus* 1993;2:227–231.
50. Wigfall DR, Sakai RS, Wallace DJ, Jordan SC. Interleukin-2 receptor expression in peripheral blood lymphocytes from systemic lupus erythematosus patients: relationship to clinical activity. *Clin Immunol Immunopathol* 1988;47:354–362.
51. Furukawa F, Tokura Y, Matsushita K, et al. Selective expansions of T cells expressing V beta 8 and V beta 13 in skin lesions of patients with chronic cutaneous lupus erythematosus. *J Dermatol* 1996;23:670–676.
52. Groen H, Aslander M, Bootsma H, van der Mark TW, Kallenberg CG, Postma DS. Bronchoalveolar lavage cell analysis and lung function impairment in patients with systemic lupus erythematosus (SLE). *Clin Exp Immunol* 1993;94:127–133.
53. Alcocer-Varela J, Aleman-Hoey D, Alarcon-Segovia D. Interleukin-1 and interleukin-6 activities are increased in the cerebrospinal fluid of patients with CNS lupus erythematosus and correlate with local late T-cell activation markers. *Lupus* 1992;1:111–117.
54. Zandman-Goddard G, Lorber M, Shoenfeld Y. Systemic lupus erythematosus and thymoma—a double-edged sword. *Int Arch Allergy Immunol* 1995;108:99–102.
55. Molina JF, Citera G, Rosler D, et al. Coexistence of human immunodeficiency virus infection and systemic lupus erythematosus. *J Rheumatol* 1995;22:347–350.
56. Byrd VM, Sergent JS. Suppression of systemic lupus erythematosus by the human immunodeficiency virus. *J Rheumatol* 1996;23:1295–1296.
57. Eisenberg RA, Winfield JB, Cohen PL. Subclass restriction of anti-Sm antibodies in MRL mice. *J Immunol* 1982;129:2146–2149.
58. Crow MK, DelGiudice-Asch G, Zehetbauer JB, et al. Autoantigen-specific T cell proliferation induced by the ribosomal P2 protein in patients with systemic lupus erythematosus. *J Clin Invest* 1994;94:345–352.
59. Okubo M, Yamamoto K, Kato T, et al. Detection and epitope analysis of autoantigen-reactive T cells to the U1-small nuclear ribonucleoprotein A protein in autoimmune disease patients. *J Immunol* 1993;151:1108–1115.
60. Hoffman RW, Takeda Y, Sharp GC, et al. Human T cell clones reactive against

U-small nuclear ribonucleoprotein autoantigens from connective tissue disease patients and healthy individuals. *J Immunol* 1993;151:6460–6469.

61. Desai-Mehta A, Mao C, Rajagopalan S, Robinson T, Datta SK. Structure and specificity of T cell receptors expressed by potentially pathogenic anti-DNA autoantibody-inducing T cells in human lupus. *J Clin Invest* 1995;95:531–541.

62. Wen L, Pao W, Fong FS, et al. Germinal center formation, immunoglobulin class switching, and autoantibody production driven by "non-alpha/beta" T cells. *J Exp Med* 1996;183:2271–2282.

63. Fujitsu T, Sakuma S, Seki N, Senoh H, Mori J, Kikuchi H. Effect of auranofin on autoimmune disease in a mouse model. *Int J Immunopharmacol* 1986;8: 897–910.

64. Hang L, Theofilopoulos AN, Balderas RS, Francis SJ, Dixon FJ. The effect of thymectomy on lupus-prone mice. *J Immunol* 1984;132:1809–1813.

65. Steinberg AD, Roths JB, Murphy ED, Steinberg RT, Raveche ES. Effects of thymectomy or androgen administration upon the autoimmune disease of MRL/Mp-*lpr/lpr* mice. *J Immunol* 1980;125:871–873.

66. Wofsy D, Ledbetter JA, Roubinian JR, Seaman WE, Talal N. Thymic influences on autoimmunity in MRL-*lpr* mice. *Scand J Immunol* 1982;16:51–58.

67. Rozzo SJ, Drake CG, Chiang B-L, Gershwin ME, Kotzin BL. Evidence for polyclonal T cell activation in murine models of systemic lupus erythematosus. *J Immunol* 1994;153:1340–1351.

68. Sobel ES, Cohen PL, Eisenberg RA. *Lpr* T cells are necessary for autoantibody production in *lpr* mice. *J Immunol* 1993;158:4160–4167.

69. Mounty JD, Zhou T, Johnson L. Production of transgenic mice and application to immunology and autoimmunity. *Am J Med Sci* 1990;300:322–329.

70. Peng SL, Fatenejad S, Craft J. Induction of nonpathologic, humoral autoimmunity in lupus-prone mice by a class II-restricted, transgenic alpha beta T cell. Separation of autoantigen-specific and -nonspecific help. *J Immunol* 1996;157: 5225–5230.

71. Sobel ES, Kakkanaiah VN, Kakkanaiah M, Cheek RL, Cohen PL, Eisenberg RA. T-B collaboration for autoantibody production in *lpr* mice is cognate and MHC-restricted. *J Immunol* 1994;152:6011–6016.

72. Peng SL, Madaio MP, Hughes DPM, et al. Murine lupus in the absence of alpha-beta T cells. *J Immunol* 1996;156:4041–4049.

73. Bernard NF, Eisenberg RA, Cohen PL. Response of MRL/Mp-+/+ mice to mouse Sm: non-H-2-linked genes determine T cell recognition. *J Immunol* 1985; 134:1422–1425.

74. Bernard NF, Eisenberg RA, Cohen PL. H-2 linked If gene control of the T cell recognition of the Sm nuclear autoantigen and the aberrant response of autoimmune MRL/Mp-+/+ mice. *J Immunol* 1985;134:3812–3818.

75. Mohan C, Adams S, Stanik V, Datta SK. Nucleosome: a major immunogen for pathogenic autoantibody-inducing T cells of lupus. *J Exp Med* 1993;177: 1367–1381.

76. Ebling FM, Tsao BP, Singh RR, Sercarz E, Hahn BH. A peptide derived from an autoantibody can stimulate T cells in the (NZB × NZW)F1 mouse model of systemic lupus erythematosus. *Arthritis Rheum* 1993;36:355–364.

77. Desai-Mehta A, Lu L, Ramsey-Goldman R, Datta SK. Hyperexpression of CD40 ligand by B and T cells in human lupus and its role in pathogenic autoantibody formation. *J Clin Invest* 1996;97:2063–2073.

78. Mohan C, Shi Y, Laman JD, Datta SK. The interaction between CD40 and its ligand gp39 in the development of murine lupus nephritis. *J Immunol* 1995;154: 1470–1480.

79. Ma J, Xu J, Madaio MP, et al. Autoimmune *lpr/lpr* mice deficient in CD40 ligand: spontaneous Ig class switching with dichotomy of autoantibody responses. *J Immunol* 1996;157:417–426.

80. Dziarski R. Preferential induction of autoantibody secretion in polyclonal activation by peptidoglycan and lipopolysaccharide: II. In vivo studies. *J Immunol* 1982;128:1026–1030.

81. Fisher DE, Reeves WH, Conner GE, Blobel G, Kunkel HG. Pulse labeling of small nuclear ribonucleoproteins in vivo reveals distinct patterns of antigen recognition by human autoimmune antibodies. *Proc Natl Acad Sci USA* 1984;81: 3185–3189.

82. Rokeach LA, Jannatipour M, Haselby JA, Hoch SO. Mapping of the immunoreactive domains of a small nuclear ribonucleoprotein-associated Sm-D autoantigen. *Clin Immunol Immunopathol* 1992;65:315–324.

83. Reeves WH, Pierani A, Chou CH, et al. Analysis of the assembly, DNA binding, and antigenicity of the Ku autoantigen using recombinant vaccinia viruses. *Mol Biol Rep* 1991;15:115.

84. Rosario MO, Fox OF, Koren E, Harley JB. Anti-Ro (SS-A) antibodies from Ro (SS-A)-immunized mice. *Arthritis Rheum* 1988;31:227–237.

85. James JA, Gross T, Scofield RH, Harley JB. Immunoglobulin epitope spreading and autoimmune disease after peptide immunization: Sm B/B'-derived PPPGMRPP and PPPGIRGP induce spliceosome autoimmunity. *J Exp Med* 1995;181: 453–461.

86. Lin RH, Mamula MJ, Hardin JA, Janeway CA. Induction of autoreactive B cells allows priming of autoreactive T cells. *J Exp Med* 1991;173:1433–1439.

87. Slobbe RL, Pruijn GJM, van Venrooij WJ. Ro (SS-A) and La (SS-B) ribonucleoprotein complexes: structure, function and antigenicity. *Ann Med Interne* 1991; 142:592–600.

88. Reynolds P, Gordon TP, Purcell AW, Jackson DC, McCluskey J. Hierarchical self-tolerance to T cell determinants within the ubiquitous nuclear self-antigen La (SS-B) permits induction of systemic autoimmunity in normal mice. *J Exp Med* 1996;184:1857–1870.

89. Fuchs S, Mozes E, Stollar BD. The nature of murine immune response to nucleic acids. *J Immunol* 1975;114:1287–1291.

90. Cooke MS, Mistry N, Wood C, Herbert KE, Lunec J. Immunogenicity of DNA damaged by reactive oxygen species—implications for anti-DNA antibodies in lupus. *Free Radic Biol Med* 1997;22:151–159.

91. Krieg AM, Yi AK, Matson S, et al. CpG motifs in bacterial DNA trigger direct B-cell activation. *Nature* 1995;374:546–549.

92. Gilkeson GS, Ruiz P, Pippen AM, Alexander AL, Lefkowith JB, Pisetsky DS. Modulation of renal disease in autoimmune NZB/NZW mice by immunization with bacterial DNA. *J Exp Med* 1996;183:1389–1397.

93. Rumore PM, Steinman CR. Endogenous circulating DNA in systemic lupus erythematosus. Occurrence as multimeric complexes bound to histone. *J Clin Invest* 1990;86:69–74.

94. Li JZ, Steinman CR. Plasma DNA in systemic lupus erythematosus. Characterization of cloned base sequences. *Arthritis Rheum* 1989;32:726–733.

95. Casciola-Rosen L, Rosen A, Petri M, Schliessel M. Surface blebs on apoptotic cells are sites of enhanced procoagulant activity: implications for coagulation events and antigenic spread in systemic lupus erythematosus. *Proc Natl Acad Sci USA* 1996;93:1624–1629.

96. Rudensky AY, Preston-Hurlburt P, Hong SC, Barlow A, Janeway CA. Sequence analysis of peptides bound to MHC class II molecules. *Nature* 1991;353: 622–627.

97. Nygard NR, Bono C, Brown LR, et al. Antibody recognition of an immunogenic influenza hemagglutinin-human leukocyte antigen class II complex. *J Exp Med* 1991;174:243–251.

98. Asherson GL. Antigen-specific T-helper and -suppressor factors in the control of the immune response. *Immunol Suppl* 1988;1:53–56.

99. Bonomo A, Kehn PJ, Shevach EM. Post-thymectomy autoimmunity: abnormal T-cell homeostasis. *Immunol Today* 1995;16:61–67.

100. Monier JC, Costa O, Souweine G, Rigal D. Lupus-like syndrome in some strains of nude mice. *Thymus* 1980;1:241–255.

101. Morse III HC, Steinberg AD, Schur PH, Reed ND. Spontaneous "autoimmune disease" in nude mice. *J Immunol* 1974;113:688–696.

102. Sy MS, Benacerraf B. Suppressor T cells, immunoglobulin and Igh restriction. *Immunol Rev* 1988;101:133–148.

103. Moller G. Do suppressor T cells exist? *Scand J Immunol* 1988;27:247–250.

104. Urdahl KB, Pardoll DM, Jenkins MK. Cyclosporine A inhibits positive selection and delays negative selection in alpha beta TCR transgenic mice. *J Immunol* 1994;152:2853–2859.

105. Alcocer-Varela J, Alarcon-Segovia D. Longitudinal study on the production of and cellular response to interleukin-2 in patients with systemic lupus erythematosus. *Rheumatol Int* 1995;15:57–63.

106. Spronk PE, ter Borg EJ, Huitema MG, Limburg PC, Kallenberg CG. Changes in levels of soluble T-cell activation markers, sIL-2R, sCD4 and sCD8, in relation to disease exacerbations in patients with systemic lupus erythematosus: a prospective study. *Ann Rheum Dis* 1994;53:235–239.

107. Hagiwara E, Gourley MF, Lee S, Klinman DM. Disease severity in patients with systemic lupus erythematosus correlates with an increased ratio of interleukin-10-interferon gamma-secreting cells in the peripheral blood. *Arthritis Rheum* 1996;39:379–385.

108. Erb KJ, Rueger B, von Brevern M, Ryffel B, Schimpl A, Rivett K. Constitutive expression of interleukin (IL)-4 in vivo causes autoimmune-type disorders in mice. *J Exp Med* 1997;185:329–339.

109. Rus V, Svetic A, Nguyen P, Gause WC, Via CS. Kinetics of Th1 and Th2 cytokine production during the early course of acute and chronic murine graft-versus-host disease. Regulatory role of donor CD8+ T cells. *J Immunol* 1995;155:2396–2406.

110. Handwerger BS, Rus V, da Silva L, Via CS. The role of cytokines in the immunopathogenesis of lupus. *Springer Semin Immunopathol* 1994;16:153–180.

111. Jacob CO, Fronek Z, Lewis GD, Koo M, Hansen JA. Heritable major histocompatibility complex class II-associated differences in production of tumor necrosis factor alpha: relevance to genetic predisposition to systemic lupus erythematosus. *Proc Natl Acad Sci USA* 1990;87:1233–1237.

112. Jacob CO, Hwang F. Definition of microsatellite size variants for TNFa and Hsp70 in autoimmune and nonautoimmune mouse strains. *Immunogenetics* 1995;36:182–188.

113. Emlen W, Niebur J, Kadera R. Accelerated in vitro apoptosis of lymphocytes form patients with systemic lupus erythematosus. *J Immunol* 1994;152: 3685–3692.

114. Gatenby PA, Irvine M. The bcl-2 proto-oncogene is overexpressed in systemic lupus erythematosus. *J Autoimmun* 1994;7:623–631.

115. Aringer M, Wintersberger W, Steiner CW, et al. High levels of bcl-2 protein in circulating T lymphocytes, but not B lymphocytes, of patients with systemic lupus erythematosus. *Arthritis Rheum* 1994;37:1423–1430.

116. Amasaki Y, Kobayashi S, Takeda T, et al. Up-regulated expression of Fas antigen (CD95) by peripheral naive and memory T cell subsets in patients with systemic lupus erythematosus (SLE): a possible mechanism for lymphopenia. *Clin Exp Immunol* 1995;99:245–250.

117. Jiang Y, Moller G. In vitro effects of HgCl2 on murine lymphocytes. I. Selective activation of T cells expressing certain V beta TCR. *Int Immunol* 1996;8: 1729–1736.

118. Wu J, Wilson J, He J, Xiang L, Schur PH, Mountz JD. Fas ligand mutation in a patient with systemic lupus erythematosus and lymphoproliferative disease. *J Clin Invest* 1996;98:1107–1113.

119. Fisher GH, Rosenberg FJ, Straus SE, et al. Dominant interfering Fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome. *Cell* 1994;81:935–946.

120. Drappa J, Vaishnaw AK, Sullivan KE, Chu JL, Elkon KB. Fas gene mutations in the Canale-Smith syndrome, an inherited lymphoproliferative disorder associated with autoimmunity. *N Engl J Med* 1996;335:1643–1649.

121. Drappa J, Brot N, Elkon KB. The Fas protein is expressed at high levels on CD4-CD8- thymocytes and activated mature lymphocytes in normal mice but not in the lupus-prone strain, MRL *lpr/lpr. Proc Natl Acad Sci USA* 1993;90:10340–10344.

122. Singer GG, Abbas AK. The Fas antigen is involved in peripheral but not thymic deletion of T lymphocytes in T cell receptor transgenic mice. *Immunity* 1994;1:365–371.

123. Russell JH, Wang R. Autoimmune *gld* mutation uncouples suicide and cytokine/proliferation pathways in activated, mature T cells. *Eur J Immunol* 1993;23:2379–2382.

124. Perkins DL, Glaser RM, Mahon CA, Michaelson J, Marshak-Rothstein A. Evidence for an intrinsic B cell defect in *lpr/lpr* mice apparent in neonatal chimeras. *J Immunol* 1990;145:549–555.

125. Katagiri T, Azuma S, Toyoda Y, et al. Tetraparental mice reveal complex cellular interactions of the mutant, autoimmunity-inducing *lpr* gene. *J Immunol* 1992;148:430–438.

126. Reap EA, Leslie D, Abrahams M, Eisenberg RA, Cohen PL. Apoptosis abnormalities of splenic lymphocytes in autoimmune *lpr* and *gld* mice. *J Immunol* 1995;154:936–943.

127. Rubio CF, Kench J, Russell DM, Yawger R, Nemazee D. Analysis of central B cell tolerance in autoimmune-prone MRL/*lpr* mice bearing autoantibody transgenes. *J Immunol* 1996;157:65–71.

128. Casiano CA, Tan EM. Recent developments in the understandng of antinuclear autoantibodies. *Int Arch Allergy Immunol* 1996;111:308–313.

129. Yoshida S, Gershwin ME. Autoimmunity and selected environmental factors of disease. *Semin Arthritis Rheum* 1993;22:399–419.

130. Yung RL, Richardson BL. Drug-induced lupus. *Rheum Dis Clin North Am* 1994;20:61–86.

131. Blomgren SE, Condemi JJ, Vaughan JH. Procainamide-induced lupus erythematosus. *Am J Med* 1972;52:338–348.

132. Rubin RL, Nusinow SR, Johnson AD, Rubenson DS, Curd JG, Tan EM. Serologic changes during induction of lupus-like disease by procainamide. *Am J Med* 1986;80:999–1002.

133. Rubin RL, McNally EM, Nusinow SR, Robinson CA, Tan EM. IgG antibodies to the histone complex H2A-H2B characterize procainamide-induced lupus. *Clin Immunol Immunopathol* 1985;36:49–59.

134. Yung RL, Johnson KJ, Richardson BC. New concepts in the pathogenesis of drug-induced lupus. *Lab Invest* 1995;73:746–759.

135. Sutton RNP, Emond RT, Thomas DB, Doniach D. The occurrence of autoantibodies in infectious mononucleosis. *Clin Exp Immunol* 1974;17:427–436.

136. Whittingham S, McNeilage J, Mackay IR. Primary Sjogren's syndrome after infectious mononucleosis. *Ann Intern Med* 1985;102:490–493.

137. Maisch B. Autoreactive mechanisms in infective endocarditis. *Springer Semin Immunopathol* 1989;11:439–456.

138. Itescu S. Rheumatic aspects of acquired immunodeficiency syndrome. *Curr Opin Rheumatol* 1996;8:346–353.

139. Johnson HM, Torres BA, Soos JM. Superantigens: structure and relevance to human disease. *Proc Soc Exp Biol Med* 1996;212:99–109.

140. de Inocencio J, Hirsch R. The role of T cells in Kawasaki disease. *Crit Rev Immunol* 1995;15:349–357.

141. East J, Prosser PR, Holborow EJ, Jaquet H. Autoimmune reactions and virus-like articles in germ-free NZB mice. *Lancet* 1967;i:755–757.

142. Hultman P, Enestrom S, Pollard KM, Tan EM. Anti-fibrillarin autoantibodies in mercury-treated mice. *Clin Exp Immunol* 1989;78:470–477.

143. Pelletier L, Pasquier R, Rossert J, Vial MC, Mandet C, Druet P. Autoreactive T cells in mercury-induced autoimmunity. *J Immunol* 1988;140:750–754.

144. Black C, Pereira S, McWhirter A, Welsh K, Laurent R. Genetic susceptibility to scleroderma-like syndrome in symptomatic and asymptomatic workers exposed to vinyl chloride. *J Rheumatol* 1986;13:1059–1062.

145. Yoshida SH, German JB, Fletcher MP, Gershwin ME. The toxic oil syndrome: a perspective on immunotoxicological mechanisms. *Regul Toxicol Pharmacol* 1994;19:60–79.

146. Kaufman LD. The eosinophilia-myalgia syndrome: current concepts and future directions. *Clin Exp Rheumatol* 1992;10:87–91.

147. Hochberg MC, Perlmutter DL, Medsger TA Jr, et al. Lack of association between augmentation mammoplasty and systemic sclerosis. *Arthritis Rheum* 1996;39:1125–1131.

148. Wong O. A critical assessment of the relationship between silicone breast implants and connective tissue diseases. *Regul Toxicol Pharmacol* 1996;23:74–85.

149. Leslie RD, Hawa M. Twin studies in auto-immune disease. *Acta Genet Med Gemellol* 1994;43:71–81.

150. Block SR, Winfield JB, Lockshin MD, D'Angelo WA, Christian CL. Studies of twins with systemic lupus erythematosus. A review of the literature and presentation of 12 additional sets. *Am J Med* 1975;59:533–552.

151. Vyse TJ, Kotzin BL. Genetic basis of systemic lupus erythematosus. *Curr Opin Immunol* 1996;8:843–851.

152. Drake CG, Rozzo SJ, Vyse TJ, Palmer E, Kotzin BL. Genetic contributions to lupus-like disease in (NZBxNZW) F1 mice. *Immunol Rev* 1995;144:51–74.

153. Tsao BP, Cantor TM, Kalunian KC, et al. Evidence for linkage of a candidate chromosome 1 region to human systemic lupus erythematosus. *J Clin Invest* 1997;99:725–731.

154. Salmon JE, Millard S, Schacter LA, et al. Fc gamma RIIA alleles are heritable risk factors for lupus nephritis in African Americans. *J Clin Invest* 1996;97:1348–1354.

155. Ruddy S. Rheumatic diseases and inherited complement deficiencies. *Bull Rheum Dis* 1996;45:6–8.

156. Hauptmann G, Tappeiner G, Schifferli JA. Inherited deficiency of the fourth component of human complement. *Immunodef Rev* 1988;1:3–22.

157. Arnett FC, Bias WB, Reveille JD. Genetic studies in Sjogren's syndrome and systemic lupus erythematosus. *J Autoimmun* 1989;2:403–413.

158. Reveille JD, Schrohenloher RE, Acton RT, Barger BO. DNA analysis of HLA-DR and DQ genes in American blacks with systemic lupus erythematosus. *Arthritis Rheum* 1989;32:1243–1251.

159. Fujisaku A, Frank MB, Neas B, Reichlin M, Harley JB. HLA-DQ gene complementation and other histocompatibility relationships in man with anti-Ro SSA autoantibody response of systemic lupus erythematosus. *J Clin Invest* 1990;86:606–611.

160. Rothfield NF, Stollar BD. The relation of immunoglobulin class, pattern of antinuclear antibody, and complement-fixing antibodies to DNA in sera from patients with systemic lupus erythematosus. *J Clin Invest* 1967;46:1785–1794.

161. Radic MZ, Weigert M. Origins of anti-DNA antibodies and their implications for B-cell tolerance. *Ann NY Acad Sci* 1995;764:384–396.

162. Shlomchik MJ, Aucoin AH, Pisetsky DS, Weigert MG. Structure and function of anti-DNA autoantibodies derived from a single autoimmune mouse. *Proc Natl Acad Sci USA* 1987;84:9150–9154.

163. Shlomchik M, Mascelli M, Shan H, et al. Anti-DNA antibodies from autoimmune mice arise by clonal expansion and somatic mutation. *J Exp Med* 1990;171:265–292.

164. Bloom DD, Davignon J-L, Cohen PL, Eisenberg RA, Clarke SH. Overlap of the anti-Sm and anti-DNA responses of MRL/Mp-*lpr/lpr* mice. *J Immunol* 1993;150:1579–1590.

165. Ibrahim SM, Weigert M, Basu C, Erikson J, Radic MZ. Light chain contribution to specificity in anti-DNA antibodies. *J Immunol* 1995;155:3223–3233.

166. Diamond B, Scharff MD. Somatic mutation of the T15 heavy chain gives rise to antibody with autoantibody specificity. *Proc Natl Acad Sci USA* 1984;81:5841–5844.

167. Behar SM, Scharff MD. Somatic diversification of the S107 (T15) Vh11 germline gene that encodes the heavy-chain variable region of antibodies to double-stranded DNA in (NZB × NZW) F1 mice. *Proc Natl Acad Sci USA* 1988;85:3970–3974.

168. Bloom DD, Davignon J-L, Retter MW, et al. V region gene analysis of anti-Sm hybridomas from MRL/Mp-*lpr/lpr* mice. *J Immunol* 1993;150:1591–1610.

169. Miller FW, Twitty SA, Biswas T, Plotz PH. Origin and regulation of a disease-specific autoantibody response. Antigenic epitopes, spectrotype stability, and isotype restriction of anti-Jo-1 autoantibodies. *J Clin Invest* 1990;85:468–475.

170. Huff JP, Roos G, Peebles CL, Houghten R, Sullivan KF, Tan EM. Insights into native epitopes of proliferating cell nuclear antigen using recombinant DNA protein products. *J Exp Med* 1990;172:419–429.

171. Patton JR, Habets W, van Venrooij WJ, Pederson T. U1 small nuclear ribonucleoprotein particle-specific proteins interact with the first and second stem-loops of U1 RNA, with the A protein binding directly to the RNA independently of the 70K and Sm proteins. *Mol Cell Biol* 1989;9:3360–3368.

172. Papoian R, Pillarisetty R, Talal N. Immunological regulation of spontaneous antibodies to DNA and RNA. II. Sequential switch from IgM to IgG in NZB/NZW F1 mice. *Immunology* 1977;32:75–79.

173. Eisenberg RA, Craven SY, Cohen PL. Isotype progression and clonality of anti-Sm autoantibodies in MRL/Mp-*lpr/lpr* mice. *J Immunol* 1987;139:728–733.

174. Rubin RL, Tang FL, Chan EK, Pollard KM, Tsay G, Tan EM. IgG subclasses of autoantibodies in systemic lupus erythematosus, Sjogren's syndrome, and drug-induced autoimmunity. *J Immunol* 1986;137:2528–2534.

175. Eisenberg RA, Winfield JB, Cohen PL. Subclass restriction of anti-Sm antibodies in MRL mice. *J Immunol* 1982;129:2146–2149.

176. Nakamura RM, Tan EM. Autoantibodies to nonhistone nuclear antigens and their clinical significance. *Hum Pathol* 1983;14:392–400.

177. Habets WJ, Hoet MH, De Jong BA, Van der Kemp A, van Venrooij WJ. Mapping of B cell epitopes on small nuclear ribonucleoproteins that react with human autoantibodies as well as with experimentally-induced mouse monoclonal antibodies. *J Immunol* 1989;143:2560–2566.

178. Kozono Y, Kotzin BL, Holers VM. Resting B cells from New Zealand Black mice demonstrate a defect in apoptosis induction following surface IgM ligation. *J Immunol* 1996;156:4498–4503.

179. Maddison PJ, Reichlin M. Quantitation of precipitating antibodies to certain soluble nuclear antigens in SLE. *Arthritis Rheum* 1977;20:819–824.

180. Budman DR, Merchant EB, Steinberg AD, et al. Increased spontaneous activity of antibody-forming cells in the peripheral blood of patients with active SLE. *Arthritis Rheum* 1977;20:829–833.

181. Hollinger FB, Sharp JT, Lidsky MD, Rawls WE. Antibodies to viral antigens in systemic lupus erythematosus. *Arthritis Rheum* 1971;14:1–10.

182. Maul GG, French BT, van Venrooij WJ, Jiminez SA. Topoisomerase I identified by scleroderma 70 antisera: enrichment of topoisomerase I at the centromere in mouse mitotic cells before anaphase. *Proc Natl Acad Sci USA* 1986;83:5145–5149.

183. Mathews MB, Bernstein RM. Myositis autoantibody inhibits histidyl-tRNA synthetase: a model for autoimmunity. *Nature* 1983;304:177–179.

184. Mamula MJ, Fox OF, Yamagata H, Harley JB. The Ro/SSA autoantigen as an immunogen. Some anti-Ro/SSA antibody binds IgG. *J Exp Med* 1986;164:1889–1901.

185. Eisenberg RA, Craven SY, Warren RW, Cohen PL. Stochastic control of anti-Sm autoantibodies in MRL/Mp-*lpr/lpr* mice. *J Clin Invest* 1987;80:691–697.

186. Hochberg MC, Boyd RE, Ahearn JM, et al. Systemic lupus erythematosus: a review of clinico-laboratory features and immunogenetic markers in 150 patients with emphasis on demographic subsets. *Medicine* 1985;64:285–295.

187. Friou GJ. Setting the scene: a historical and personal view of immunologic diseases, autoimmunity, and ANA. *Clin Exp Rheumatol* 1994;12[Suppl 11]:S23–S25.

188. Friou GJ. Antinuclear antibodies: diagnostic significance and methods. *Arthritis Rheum* 1967;10:151–159.

189. Lefkowith JB, Gilkeson GS. Nephritogenic autoantibodies in lupus. *Arthritis Rheum* 1996;39:894–903.

190. Koffler D, Agnello V, Carr RI, Kunkel HG. Anti-DNA antibodies and the renal lesions of patients with systemic lupus erythematosus. *Transplant Proc* 1969;1:933–938.

191. Lee LA, Gaither KK, Coulter SN, Norris DA, Harley JB. Pattern of cutaneous immunoglobulin G deposition in subacute cutaneous lupus erythematosus is reproduced by infusing purified anti-Ro (SSA) autoantibodies into human skin-grafted mice. *J Clin Invest* 1989;83:1556–1562.

192. Buyon JP, Ben-Chetrit E, Karp S, et al. Acquired congenital heart block: pattern of maternal antibody response to biochemically defined antigens of the SSA/Ro-SSB/La system in neonatal lupus. *J Clin Invest* 1989;84:627–634.

193. Elkon K, Weissbach H, Brot N. Central nervous system function in systemic lupus erythematosus. *Neurochem Res* 1990;15:401–406.

194. Palmer DG. The anatomy of the rheumatoid lesion. *Br Med Bull* 1995;51:286–295.

195. Salmon M, Gaston JS. The role of T-lymphocytes in rheumatoid arthritis. *Br Med Bull* 1995;51:332–345.

196. DeKeyser F, Elewaut D, Vermeesch J, DeWever N, Cuvelier C, Veys EM. The role of T cells in rheumatoid arthritis. *Clin Rheumatol* 1995;14[Suppl 2]:5–9.

197. Winchester RJ, Gregersen PK. The molecular basis of susceptibility to rheumatoid arthritis: the conformational equivalence hypothesis. *Springer Semin Immunopathol* 1988;10:119–139.

198. Smiley JD, Hoffman WL, Moore SE, Paradies LH. The humoral immune response of the rheumatoid synovium. *Semin Arthritis Rheum* 1985;14:151–162.

199. Winchester RJ, Agnello V, Kunkel HG. Gamma globulin complexes in synovial fluids of patients with rheumatoid arthritis. Partial characterization and relationship to lowered complement levels. *Clin Exp Immunol* 1970;6:689–706.

200. Paliard X, West SG, Lafferty JA, et al. Evidence for the effects of a superantigen in rheumatoid arthritis. *Science* 1991;253:325–329.

201. Vaughan JH, Fox RI, Abresch RJ, Tsoukas CD, Curd JG, Carson DA. Thoracic duct drainage in rheumatoid arthritis. *Clin Exp Immunol* 1984;58:645–653.

202. Sany J. Immunological treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 1990;8[Suppl 5]:81–88.

203. Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. *Annu Rev Immunol* 1996;14:397–440.

204. Fox DA. Biological therapies: a novel approach to the treatment of autoimmune disease. *Am J Med* 1995;99:82–88.

205. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. *Lancet* 4997;344:1105–1110.

206. Nabozny GH, David CS. The immunogenetic basis of collagen induced arthritis in mice: an experimental model for the rational design of immunomodulatory treatments of rheumatoid arthritis. *Adv Exp Med Biol* 1994;347:55–63.

207. Ronnelid J, Klareskog L. Local versus sytemic immunoreactivity to collagen and the collagen-like region of C1q in rheumatoid arthritis and SLE. *Scand J Rheumatol* 1995;101[Suppl]:57–61.

208. Zvaifler NJ, Firestein GS. Pannus and pannocytes. Alternative models of joint destruction in rheumatoid arthritis. *Arthritis Rheum* 1994;37:783–789.

209. Hughes RA, Keat AC. Reiter's syndrome and reactive arthritis: a current view. *Semin Arthritis Rheum* 1994;24:190–210.

210. Lopez-Larrea C, Gonzalez-Roces S, Alvarez V. HLA-B27 structure, function, and disease association. *Curr Opin Rheumatol* 1996;8:296–308.

211. Careless DJ, Inman RD. Etiopathogenesis of reactive arthritis and ankylosing spondylitis. *Curr Opin Rheumatol* 1995;7:290–294.

212. Geczy AF, Sullivan JS. Possible role of HLA-B27 associated cytotoxic T lymphocyte activity in the pathogenesis of the seronegative arthropathies. *Ann Rheum Dis* 1995;54:329–330.

213. Kaye BR. Rheumatologic manifestations of infection with human immunodeficiency virus (HIV). *Ann Intern Med* 1989;111:158–167.

214. Taurog JD, Hammer RE. Experimental spondyloarthropathy in HLA-B27 transgenic rats. *Clin Rheumatol* 1996;15[Suppl 1]:22–27.

215. Khare SD, Luthra HS, David CS. Spontaneous inflammatory arthritis in HLA-B27 transgenic mice lacking beta 2-microglobulin: a model of human spondyloarthropathies. *J Exp Med* 1995;182:1153–1158.

216. Bacon PA. Systemic vasculitis syndromes. *Curr Opin Rheumatol* 1993;5:5–10.

217. Mader R, Keystone EC. Infections that cause vasculitis. *Curr Opin Rheumatol* 1992;4:35–38.

218. Sunday JS, Haynes BF. Pathogenic mechanisms of vessel damage in vasculitis syndromes. *Rheum Dis Clin North Am* 1995;21:861–881.

219. Invernizzi F, Pietrogrande M, Sagramoso B. Classification of the cryoglobulinemic syndrome. *Clin Exp Rheumatol* 1995;13[Suppl]13:S123–S128.

220. Hoffman GS, Kerr GS, Leavitt RY. Wegener's granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992;116:488–498.

221. Gross WL, Schmitt WH, Csernok E. ANCA and associated diseases: immunodiagnostic and pathogenetic aspects. *Clin Exp Immunol* 1993;91:1–12.

222. Price EJ, Venables PJ. The etiopathogenesis of Sjogren's syndrome. *Semin Arthritis Rheum* 1995;25:117–133.

223. Bruze M, Krook G, Ljunggren B. Fatal connective tissue disease with antinuclear antibodies following PUVA therapy. *Acta Derm Venereol* 1984;64:157–160.

224. Van Rappard-Van der Veen FM, Kiesel U, Poels L, et al. Further evidence against random polyclonal antibody formation in mice with lupus-like graft-vs-host disease. *J Immunol* 1984;132:1814–1820.

225. Morris SC, Cheek RL, Cohen PL, Eisenberg RA. Autoantibodies in chronic graft versus host result from cognate T-B interactions. *J Exp Med* 1990;171:503–517.

226. Stastny P, Stembridge VA, Ziff M. Homologous disease in the adult rat, a model for autommune disease. I. General features and cutaneous lesions. *J Exp Med* 1963;118:635–648.

227. Kennedy MJ, Hess AD. Autologous graft-versus-host disease. *Med Oncol* 1995;12:149–156.

228. Smiley JD. The many faces of scleroderma. *Am J Med Sci* 1992;304:319–333.

229. White B. Immunologic aspects of scleroderma. *Curr Opin Rheumatol* 1995;7:541–545.

230. Weiner ES, Earnshaw WC, Senecal J-L, Bordwell B, Johnson P, Rothfield NF. Clinical associations of anticentromere antibodies and antibodies to topoisomerase I: a study of 355 patients. *Arthritis Rheum* 1988;31:378–385.

231. Gershwin ME, Abplanalp H, Castles JJ, et al. Characterization of a spontaneous disease of white leghorn chickens resembling progressive systemic sclerosis. *J Exp Med* 1981;153:1640–1659.

232. Cohen PL, Eisenberg RA. *Lpr* and *gld*: single gene models of systemic autoimmunity and lymphoproliferative disease. *Annu Rev Immunol* 1991;9:243–269.

233. Izui S, Kelley VE, Masuda K, Yoshida H, Roths JB, Murphy ED. Induction of various autoantibodies by mutant gene *lpr* in several strains of mice. *J Immunol* 1984;133:227–233.

234. Perkins DL, Glaser RM, Mohan CA, Michaelson J, Marshak-Rothstein A. Evidence for an intrinsic B cell defect in *lpr/lpr* mice apparent in neonatal chimerias. *J Immunol* 1990;145:549–555.

235. Jevnikar AM, Grusby JJ, Glimcher LH. Prevention of nephritis in major histocompatibility complex class II-deficient MRL-*lpr* mice. *J Exp Med* 1994;179:1137–1143.

236. Koh D-R, Ho A, Rahemtulla A, Fung-Leung WP, Griesser H, Mak T-W. Murine lupus in MRL/*lpr* mice lacking CD4 or CD8 T cells. *Eur J Immunol* 1995;25:2558–2562.

237. Maldonado MA, Eisenberg RA, Roper E, Cohen PL, Kotzin BL. Greatly reduced lymphoproliferation in *lpr* mice lacking major histocompatibility complex class I. *J Exp Med* 1995;181:641–648.

238. Theofilopoulos AN, Dixon FJ. Murine models of systemic lupus erythematosus. *Adv Immunol* 1985;37:269–390.

239. Datta SK. A search for the underlying mechanisms of systemic autoimmune disease in the NZB × SWR model. *Clin Immunol Immunopathol* 1989;51:141–156.

240. Reininger L, Winkler TH, Kalbere CP, Jourdan M, Melchers F, Rolink AG. Intrinsic B cell defects in NZB and NZW mice contribute to systemic lupus erythematosis in (NZB × NZW) F1 mice. *J Exp Med* 1996;184:853–861.

241. Izui S, Iwamoto M, Fossati L, Merino R, Takahashi S, Ibnou-Zekri N. The Yaa gene product in systemic lupus erythematosus. *Immunol Rev* 1995;144:137–156.

242. Merino R, Fossati L, Lacour M, Lemoine R, Higaki M, Izui S. H-2-linked control of the Yaa gene-induced acceleration of lupus-like autoimmune disease in BXSB mice. *Eur J Immunol* 1992;22:295–299.

243. Satoh M, Kumar A, Kanwar YS, Reeves WH. Anti-nuclear antibody production and immune-complex glomerulonephritis in BALB/c mice treated with pristane. *Proc Natl Acad Sci USA* 1995;92:10934–10938.

244. Satoh M, Hamilton KJ, Ajmani AK, et al. Autoantibodies to ribosomal P antigens with immune complex glomerulonephritis in SJL mice treated with pristane. *J Immunol* 1996;157:3200–3206.

245. Shoenfeld Y, Mozes E. Pathogenic idiotypes of autoantibodies in autoimmunity: lessons from new experimental models of SLE. *FASEB J* 1990;4:2646–2651.

246. Fricke H, Mendlovic S, Blank M, Shoenfeld Y, Ben-Bassat M, Mozes E. Idiotype specific T-cell lines inducing experimental systemic lupus erythematosus in mice. *Immunology* 1991;73:421–427.

247. Kozlowski M, Mlinaric-Rascan I, Feng GS, Shen R, Pawson T, Siminovitch KA. Expression and catalytic activity of the tyrosine phosphatase PTP1C is severely impaired in motheaten and viable motheaten mice. *J Exp Med* 1993;178:2157–2163.

248. Letterio JJ, Geiser AG, Kulkarni AB, et al. Autoimmunity associated with TGF-beta1-deficiency in mice is dependent on MHC class II antigen expression. *J Clin Invest* 1996;98:2109–2119.

249. Marengere LE, Waterhouse P, Duncan GS, Mittrucker HW, Feng GS, Mak TW. Regulation of T cell receptor signaling by tyrosine phosphatase SYP association with CTLA-4. *Science* 1996;272:1170–1173.

250. Sadlack B, Merz H, Schorle H, Schimpl A, Feller AC, Horak I. Ulcerative colitis-like disease in mice with a disrupted interleukin-2 gene. *Cell* 1993;75:203–205.

251. Kuhn R, Lohler J, Rennick D, Rajewsky K, Muller W. Interleukin-10-deficient mice develop chronic enterocolitis. *Cell* 1993;75:263–274.

252. Mombaerts P, Mizoguchi E, Grusby MJ, Glimcher LH, Bhan AK, Tonegawa S. Spontaneous development of inflammatory bowel disease in T cell receptor mutants. *Cell* 1993;75:203–205.

253. Strasser A, Whittingham S, Vaux DL, et al. Enforced BCL2 expression in B-lymphoid cells prolongs antibody responses and elicits autoimmune disease. *Proc Natl Acad Sci USA* 1991;88:8661–8665.

254. Reap EA, Felix NJ, Wolthusen PA, Kotzin BL, Eisenberg RA. bcl-2 transgenic *lpr* mice show profound enhancement of lymphadenopathy. *J Immunol* 1995;155:5455–5462.

255. Green MD, Sweet HO, Bunker LE. Tight-skin, a new mutation of the mouse causing excessive growth of connective tissue and skeleton. *Am J Pathol* 1976;892:493–512.

256. Hatakeyama A, Kasturi KN, Wolf I, Phelps RG, Bona CA. Correlation between the concentration onf serum anti-topoisomerase I autoantibodies and histological and biochemical alterations in the skin of tight skin mice. *Cell Immunol* 1996;167:135–140.

257. Wallace VA, Kondo S, Kono T, et al. A role for CD4+ T cells in the pathogenesis of skin fibrosis in tight skin mice. *Eur J Immunol* 1994;24:1463–1466.

258. Houri JM, O'Sullivan FX. Animal models in rheumatoid arthritis. *Curr Opin Rheumatol* 1995;7:201–205.

259. Cromartie WJ, Craddock JG, Schwab JH, Anderle SK, Yang CH. Arthritis in rats after systemic injection of streptococcal cells or cell walls. *J Exp Med* 1977;146:1585–1602.

260. Stimpson SA, Esser RE, Carter PB, Sartor RB, Cromartie WJ, Schwab JH. Lipopolysaccharide induces recurrence of arthritis in rat joints previously injured by peptidoglycan-polysaccharide. *J Exp Med* 1987;165:1688–1702.

261. Castro JE, Listman JA, Jacobson BA, et al. Fas modulation of apoptosis during negative selection of thymocytes. *Immunity* 1996;5:617–627.

262. Naboczny GH, David CS. Collagen arthritis in T cell receptor congenic mice. A unique approach to study the role of T cell receptor genotypes in autoimmune arthritis. *Adv Exp Med Biol* 1995;383:99–104.

263. Iwakura Y, Tosu M, Yoshida E, et al. Induction of inflammatory arthropathy resembling rheumatoid arthritis in mice transgenic for HTLV-1. *Science* 1991;253:1026–1028.

264. Green JE, Hinrich SH, Vogel J, Jay G. Endocrinopathy resembling Sjogren's syndrome in HTLV-1 tax transgenic mice. *Nature* 1989;341:72–74.

265. Nishioka K, Maruyama I, Sato K, Kitajima I, Nakajima T, Osame M. Chronic inflammatory arthopathy associated with HTLV-1. *Lancet* 1989;i:441–441.

266. Brennan FM. Transgenic models for arthritis: useful clues to be gained? *Ann Med* 1996;28:271–274.

267. Wang Y, Hu Q, Madri JA, Rollins SA, Chodra A, Matis LA. Amelioration of lupus-like autoimmune disease in NZB/W F1 mice after treatment with a blocking monoclonal antibody specific for complement component C5. *Proc Natl Acad Sci USA* 1996;93:8563–8568.

268. Koffler D, Schur PH, Kunkel HG. Immunological studies concerning the nephritis of systemic lupus erythematosus. *J Exp Med* 1967;126:607–624.

269. Mukherjee R, Zhang Z, Zhong R, Yin Z-Q, Roopenian DC, Jevnikar AM. Lupus nephritis in the absence of renal major histocompatibility complex class I and class II molecules. *J Am Soc Nephrol* 1996;7:2445–2452.

270. Roubey RAS. Immunology of the antiphospholipid antibody syndrome. *Arthritis Rheum* 1996;39:1444–1454.

271. Kagnoff MF. Oral tolerance: mechanisms and possible role in inflammatory joint diseases. *Baillieres Clin Rheumatol* 1996;10:41–54.